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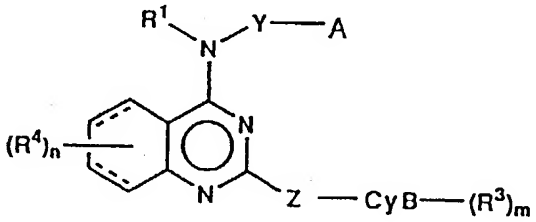
(54) 4-Aminoquinazoline derivatives, and their use as medicine.

(57) The compounds of the formula :



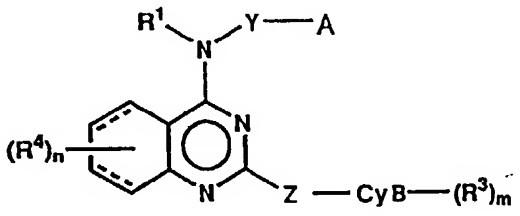
(I)

wherein R^1 is H or alkyl ;
Y is bond or alkylene ;
A is
(i) -CyA-(R^2)l,
(ii) -O-R^0 or -S(O)p-R^0 or
(iii) -$NR^{16}R^{17}$;
CyA is
(1) 3-7 membered monocyclic carbocyclic ring,
(2) 4-7 membered monocyclic hetero ring containing as hetero atoms, one N atom, one N and one O atoms, two N and one O atoms, or one N and two O atoms,
(3) 4-7 membered monocyclic hetero ring containing as hetero atoms, 1 or 2 O or S atoms ;
R^2 is (1) H, (2) alkyl, (3) alkoxy, (4) -$COOR^5$, in which R^5 is H or alkyl, (5) -NR^6R^7, (6) -$SO_2NR^6R^7$, (7) halogen, (8) CF_3, (9) NO_2 or (10) CF3O ;
Z is bond, methylene, ethylene, vinylene or ethynylene ;
R^3 is H, alkyl, alkoxy, halogen or CF_3 ;
and acid addition salts thereof, salts thereof, and hydrates thereof ; have inhibitory effect on cGMP-PDE, or additionally on TXA_2 synthetase.

EP 0 579 496 A1

The present invention relates to novel 4-aminoquinazoline derivatives. More particularly, this invention relates to:

(i) 4-aminoquinazoline derivatives of the following formula:



(I)

wherein all of the symbols have the same meanings as described hereinafter, and the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, which have inhibitory activity on cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally on thromboxane A_2 synthetase,

(ii) processes for the preparation thereof,

(iii) inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase, or additionally of thromboxane A_2 synthetase containing them, and

(iv) methods of prophylactic and curative treatment of mammals, including humans, by administering an effective amount of the compounds of the formula (I), the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, to the patient to be treated.

Cyclic guanosine 3',5'-monophosphate (abbreviated as cGMP hereafter) was found in urine in rats by D. F. Ashman in 1963. Till now, it has been known that cGMP is distributed broadly in tissues of any animals including human beings. cGMP is biosynthesized from guanosine triphosphate (GTP) by the action of guanylate cyclase.

cGMP has been experimentally confirmed to have various physiological activities. For example, cGMP induces the relaxation of heart muscle and of smooth muscle. Further, it is related to the formation of neuronal synapses, and it acts as a trigger of cell proliferation and it induces the proliferation of lymphocyte.

cGMP is metabolized to physiologically inactive 5'-GMP by the action of cGMP phosphodiesterase (abbreviated as cGMP-PDE hereafter).

Accordingly, the inhibition of the action of cGMP-PDE is considered to be useful for the prevention and/or treatment of diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, pulmonary hypertension, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency.

On the other hand, thromboxane A_2 (abbreviated as TXA_2 hereafter) was found as a constituent of the arachidonate cascade, in platelets by M. Hamberg in 1975. TXA_2 is biosynthesized from arachidonic acid released from cell membrane via prostaglandin G_2 and prostaglandin H_2, and rapidly metabolized to inactive thromboxane B_2. TXA_2 is known to induce platelet aggregation and to contract smooth muscle, particularly blood vessel muscle and bronchial muscle. TXA_2 synthetase was isolated and purified from microsome in platelets.

Accordingly, the inhibition of TXA_2 synthetase decreases the biosynthesis of TXA_2, and is useful for the prevention and/or treatment of inflammation, hypertension, thrombosis, arteriosclerosis, cerebral apoplexy, asthma, myocardial infarction, cardiostenosis, cerebral infarction, etc.

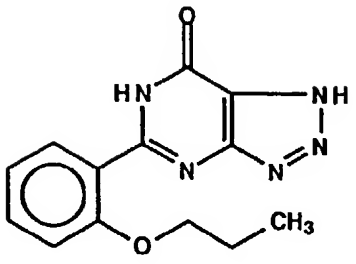
It is considered that almost any disease occurs by the complex interaction of plural mechanisms. Accordingly, the inhibition of any one of the plural mechanism is not adequate to treat a disease. A medicament inhibiting as many mechanisms as possible, which induce the disease, is considered to be effective and ideal.

Especially, it is very useful for the prevention and/or treatment of diseases induced by platelet aggregation, e.g. angina pectoris, heart failure, plumonary hypertension and various kinds of renal diseases to have inhibitory active on both cGMP PDE and TXA_2 synthetase.

Related Arts

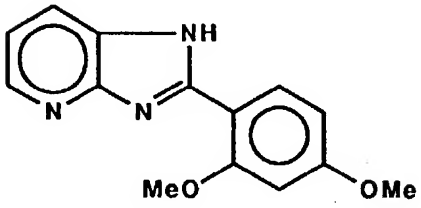
Up to now, some compounds have been known as cGMP-PDE inhibitors, for example,

Zaprinast



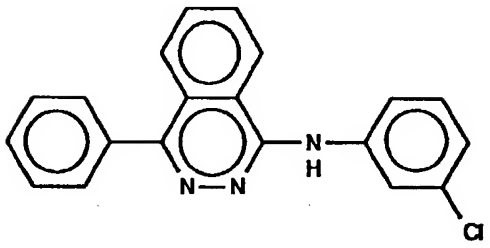
(A)

AR-L 57



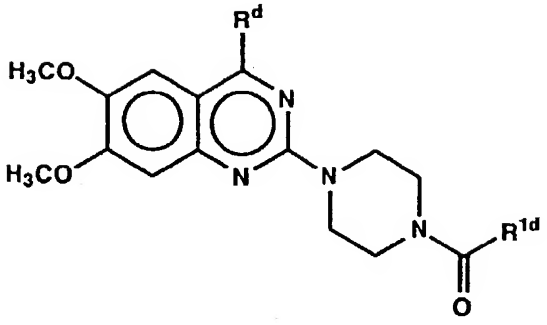
(B)

MY-5445



(C)

Many compounds derived from the above lead compounds have been proposed and many patent applications relating to those have been filed. For example, as derivatives of Zaprinast, compounds wherein the 1H-1,2,3-triazole skeleton is replaced by various other hetero cycles (see USP-5047404), those wherein the triazole is replaced by a benzene ring (see EP-371731), and those wherein the triazole is eliminated, i.e. those having only the pyrimidine skeleton (see EP-395328), have been proposed. The above mentioned compounds always contain an oxo group at the 4th position of the pyrimidine skeleton. The compounds having an amino group at the said position are described in USP-4060615. The specification discloses 4-amino-6,7-dimethoxy-2-piperazinylquinazoline derivatives of the following formula:

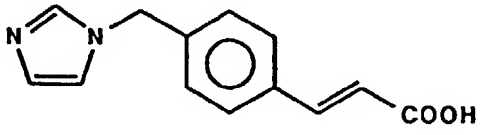


(D)

wherein R^d is amino or hydrazino,
R^{1d} is C3-8 cycloalkyl, C3-8 methylcycloalkyl or C4-8 cycloalkenyl,
and their acid addition salts.

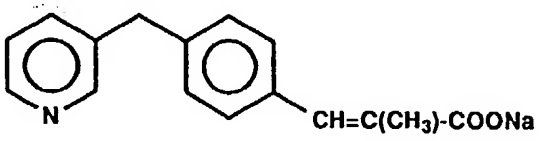
Furthermore, some TXA_2 synthetase inhibitors have been known, for example,

OKY-046



(E)

ONO-1581



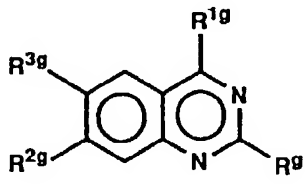
(F)

Many derivatives containing an imidazole or pyridine ring as the basic skeleton have been proposed. However, there appears to be no TXA_2 synthetase inhibitor having both the said ring and quinazoline ring.

On the other hand, many compounds having a quinazoline ring as the skeleton, which are not known to have inhibitory activity on cGMP-PDE and/or on TXA_2 synthetase, have been proposed.

For example, as to 4-aminoquinazoline derivatives having cyclic groups at the 2nd position thereof and as N-substituent,

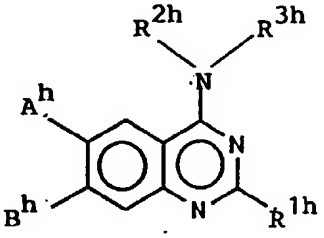
(1) USP-3772295 discloses the compounds of the formula:



(G)

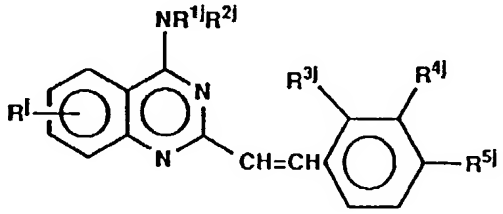
wherein R^{1g} is cyclopentylamino, trifluoromethylanilino, furfurylamino, 3-furylmethylamino, tetrahydrofur-

furylamino or tetrahydro-3-furylmethylamino etc;
R^g is hydrogen, phenyl substituted by one or more methyl, methoxy, chlorine, fluorine or methylenedioxy, a residue derived from furan, thiophene, pyridine, picoline, benzofuran or benzothiophene, or naphthyl;
R^{2g} and R^{3g} are hydrogen or chlorine;
and their acid addition salts, being useful as diuretics,
(2) GBP-1199768 discloses the compounds of the formula:



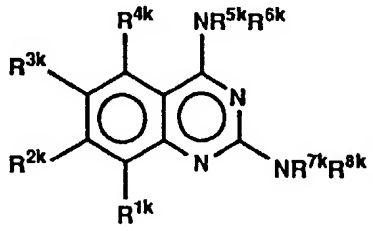
(H)

wherein each A^h and B^h are C1-5 alkoxy, hydrogen, hydroxy, methyl etc. provided that both A^h and B^h are not hydrogen;
R^{1h} is phenyl, benzyl, phenethyl or substituted phenyl etc.;
each R^{2h} and R^{3h} are hydrogen, phenyl, phenylalkyl etc.;
and their acid addition salts, being useful as hypotensives or bronchodilators,
(3) Soviet Union Patent No. 461621 discloses the compounds of the formula:



(J)

wherein R^j is hydrogen, lower alkyl or lower alkoxy;
R^{1j} is hydrogen or lower alkyl;
R^{2j} is phenyl etc.;
R^{3j}, R^{4j} and R^{5j} are hydrogen, halogen, nitro etc.;
and their salts, being useful as a medicine;
(4) WO-8905297 discloses the compounds of the formula:

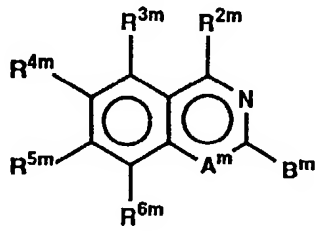


(K)

wherein each R^{1k}, R^{2k}, R^{3k} and R^{4k} are hydrogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, halogen, trifluoromethyl etc.;
each R^{5k} and R^{6k} are hydrogen, C1-4 alkyl, $-(CH_2)_nAr$ in which n is 0-4 and Ar is optionally substituted phenyl, etc.;
R^{7k} and R^{8k}, taken together with a nitrogen to which these groups bond, are saturated or unsaturated carbocyclic ring, etc.;
and their salts; having inhibitory effect on H^+K^+ATPase and being useful as antiulcer agents.

As to 4-aminoquinazoline derivatives having a cyclic group at the 2nd position thereof or as N-substituent,

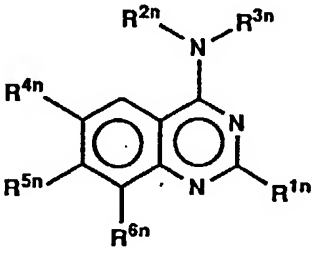
(5) USP-4269834 discloses a complex of a copper salt (III) and the compounds of the formula:



(M)

wherein A^m is nitrogen etc.;
B^m is 2-optionally substituted-6-pyridyl or 1,5-optionally substituted-2-imidazolyl;
R^{2m} is amino, alkylamino, dialkylamino etc.;
each R^{3m}, R^{4m} R^{5m} and R^{6m} are hydrogen, halogen, alkyl etc.;
and their acid addition salts, being useful as agents for the treatment of mycoplasma infections,

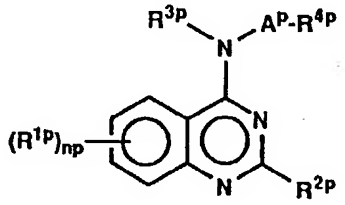
(6) USP-3819628 discloses the compounds of the formula:



(N)

wherein R^{1n} is optionally substituted phenyl;
each R^{2n} and R^{3n} are hydrogen, C1-4 alkyl, $-CH_2(CH_2)_mONO_2$ etc.;
each R^{4n}, R^{5n} and R^{6n} are hydrogen, C1-3 alkyl, C1-3 alkoxy etc,;
provided that more than two groups are not alkyl;
and their salts; being useful as anti-angina agents,

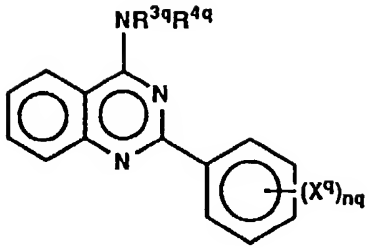
(7) USP-3971783 discloses the compounds of the formula:



(P)

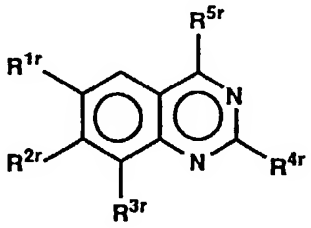
wherein R^{1p} is halogen, lower alkyl, lower alkoxy etc.;
R^{2p} is hydrogen, halogen, lower alkyl, lower alkoxy-lower alkyl etc.;
R^{3p} is hydrogen, lower alkyl etc.;
R^{4p} is aromatic N-containing heterocyclic;
AP is C1-4 alkylene;
np is 0-3;
and their acid addition salts; being useful as cardiac stimulants,

(8) USP-4306065 discloses the compounds of the formula:



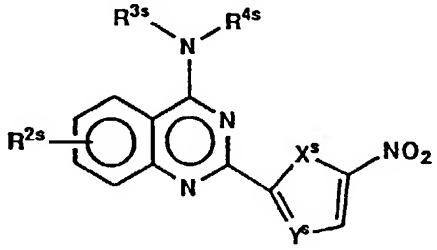
(Q)

wherein R^{3q} is 4-cyanocycloalkyl-alkyl etc.;
R^{4q} is hydrogen or alkyl;
X^q is hydrogen, alkyl, alkoxy, nitro, amino or halogen;
nq is 1-3;
and their acid addition salts and hydrates; being useful as hypotensives,
(9) JP Kokai No. 58-172379 discloses the compounds of the formula:



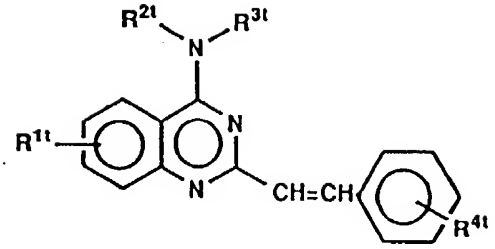
(R)

each R^{1r} and R^{3r} are lower alkyl;
R^{2r} is optionally branched alkoxycarbonyl;
R^{4r} is hydrogen, alkyl or phenyl;
R^{5r} is amino, alkylamino, dialkylamino etc; being useful as vasodilators,
(10) Swiss Patent No. 578556 discloses the compounds of the formula:



(S)

wherein R^{3s} is hydrogen, lower alkyl etc.;
R^{4s} is hydrogen, amino, lower hydroxyalkyl, lower alkyl etc.;
R^{2s} is hydrogen, lower alkyl, lower alkoxy etc.;
X^s is -O-, -S- or -N= and Y^s is -N=, or X^s is -N= and Y^s is -CH=;
and their acid addition salts; having bactericidal activity,
(11) USP-3753981 discloses the compounds of the formula:



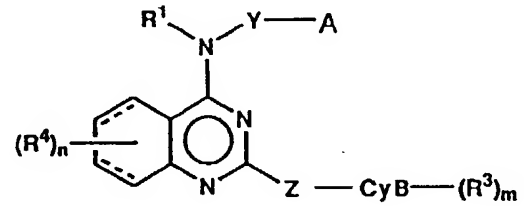
(T)

wherein R^{1t} is hydrogen, lower alkyl, lower alkoxy etc.;
each R^{2t} and R^{3t} are hydrogen, lower alkyl, hydroxy-(lower alkyl) etc.;
and their acid addition salts; having anti-inflammatory activity.

Energetic investigation has been carried out in order to discover compounds having inhibitory activities on cGMP-PDE or additionally TXA_2 synthetase, and as a result, the present inventors have found the compound of the present invention.

There is no description of compounds of the formula (I) in any of the related art disclosing compounds in the formulae (D) and (G) to (T) mentioned above. Accordingly, the compounds of the present invention are quite novel. Furthermore, the fact that compounds of the present invention have inhibitory activity on cGMP-PDE or additionally TXA_2 synthetase, is not suggested from pharmaceutical use disclosed in any of the related art mentioned above. Additionally, the inhibitory activity on cGMP-PDE or TXA_2 synthetase, of the compounds of the present invention, is superior to that of the compounds described in any of the related art mentioned above.

The present invention relates to:
(i) quinazoline derivatives of the formula:



(I)

wherein R^1 is hydrogen or C1-4 alkyl;
Y is single bond or C1-6 alkylene;
A is
(i) -CyA-(R^2)l,
(ii) -O-R^0 or -S(O)p-R^0,
(iii) -$NR^{16}R^{17}$;
in which R^0 is hydrogen, C1-4 alkyl. hydroxy-C1-4 alkyl or -CyA-(R^2)l ;
R^{16} and R^{17} independently are hydrogen or C1-4 alkyl;
p is 0-2;
CyA is
(1) carbocyclic mono-ring of 3-7 membered, saturated or unsaturated,
(2) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,
(3) heterocyclic mono-ring of 4-7 membered containing one nitrogen and one oxygen, unsaturated or partially saturated,
(4) heterocyclic mono-ring of 4-7 membered containing one nitrogen and two oxygen, unsaturated or partially saturated,
(5) heterocyclic mono-ring of 4-7 membered containing two nitrogen and one oxygen, unsaturated or partially saturated,
(6) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated or
(7) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated, fully or partially

saturated or saturated;

R^2 is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -$COOR^5$, in which R^5 is hydrogen or C1-4 alkyl, (5) -NR^6R^7, in which R^6 and R^7 independently are hydrogen or C1-4 alkyl, (6) -$SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;

Z is single bond, methylene, ethylene (CH_2CH_2), vinylene (CH=CH) or ethynylene (C≡C);

CyB is

(1) heterocyclic mono-ring of 4-7 membered containing one nitrogen, unsaturated or partially saturated,

(2) heterocyclic mono-ring of 4-7 membered containing two nitrogen , unsaturated or partially saturated,

(3) heterocyclic mono-ring of 4-7 membered containing three nitrogen, unsaturated or partially saturated,

(4) heterocyclic mono-ring of 4-7 membered containing one or two oxygen, unsaturated or partially saturated, or

(5) heterocyclic mono-ring of 4-7 membered containing one or two sulfur, unsaturated or partially saturated;

R^3 is hydrogen, C1-4 alkyl, C1-4 alkoxy, halogen or trifluoromethyl;

R^4 is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -$COOR^8$, in which R^8 is hydrogen or C1-4 alkyl, (5) -NR^9R^{10}, in which R^9 is hydrogen, C1-4 alkyl or phenyl(C1-4 alkyl) and R^{10} is hydrogen or C1-4 alkyl, (6) -$NHCOR^{11}$, in which R^{11} is C1-4 alkyl, (7) -$NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined, (9) -$OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -SO2N=$CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1-4 alkyl and R^{13} is C1-4 alkyl, (16) -$CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1-4 alkyl or phenyl(C1-4 alkyl) and R^{15} is C1-4 alkyl or (17) C1-4 alkylthio, (18) C1-4 alkylsulfinyl, (19) C1-4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl)silylethynyl or (23) acetyl;

and l, m and n independently are 1 or 2;

with the proviso that

(1) the group of the formula: -CyA-$(R^2)_l$ does not represent a cyclopentyl or trifluoromethylphenyl group when Y is a single bond, that

(2) a CyB ring should not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that

(3) a CyB ring should not represent pyridine or thiophene when CyA is a ring of CyA-(7) and that

(4) Y is not a single bond, when A is (ii) -O-R^0 or -S(O)p-R^0 or (iii) -$NR^{16}R^{17}$; and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, and hydrates thereof,

(ii) process for the preparation thereof,

(iii) cGMP-PDE inhibitors, or additionally TXA_2 synthetase inhibitors, containing them as active ingredient, and

(iv) methods of prophylactic and curative treatment of mammals, including humans, by administering an effective amount of the compounds of the formula (I), the pharmaceutically acceptable acid addition salts thereof, the pharmaceutically acceptable salts thereof, and the hydrates thereof, to the patient to be treated.

In the formula (I), the C1-4 alkyl group represented by R^0,R^1,R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} mean methyl, ethyl, propyl, butyl and the isomers thereof.

In the formula (I), the C1-4 alkoxy group represented by R^2, R^3 and R^4 mean methoxy, ethoxy, propoxy, butoxy and isomers thereof.

In the formula (I), the halogen atom represented by R^2, R^3 and R^4 mean fluorine, chlorine, bromine and iodine.

In the formula (I), the C1-6 alkylene group represented by Y means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

In the formula (I), examples of 3-7 membered, saturated or unsaturated, monocyclic carbocyclic ring, represented by CyA-(1), are cyclobutadiene, cyclopentadiene, benzene, cycloheptatriene ring, and partially or fully saturated rings thereof, for example, cyclobutane, cyclopentane, cyclohexane, cycloheptane ring, and cyclopropane ring.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom, unsaturated or partially saturated represented by CyA-(2) and CyB-(1) is, for example, azepine, pyridine, pyrrole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(3) is, for example, oxyazepine, oxazine, oxyazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one nitrogen atom and two oxygen atom, unsaturated or partially saturated represented by CyA-(4) is, for example, dioxazepine, dioxazine, dioxazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two nitrogen atom and one oxygen atom, unsaturated or partially saturated represented by CyA-(5) is, for example, oxadiazepine, oxadiazine, oxadiazole, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one or two sulfur atom, unsaturated or partially saturated represented by CyA-(6) and CyB-(5) is, for example, thiepin, thiophene, thiain, dithian, isomeric rings thereof and partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two oxygen atoms, unsaturated or fully or partially saturated represented by CyA-(7) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof and fully or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing one or two oxygen atoms, unsaturated or partially saturated represented by CyB-(4) is, for example, oxepin, pyran, dioxin, furan, isomeric rings thereof or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing two nitrogen atoms, unsaturated or partially saturated represented by CyB-(2) is, for example, diazepine, diazine, diazole, isomeric rings thereof or partially saturated rings thereof.

In the formula (I), heterocyclic mono-ring of 4-7 membered containing three nitrogen atoms, unsaturated or partially saturated represented by CyB-(3) is, for example, triazepine, triazine, triazole, isomeric rings thereof and partially saturated rings thereof.

Examples of representative compounds of the present invention are listed as follows:

1 4-phenylmethylamino-2-(3-pyridyl)quinazoline,
2 4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
3 4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4 4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
5 4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
6 4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)-quinazoline,
7 4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
8 4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
9 4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
10 4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
11 4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,
12 4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,
13 4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
14 4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,
15 4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
16 4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,
17 4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
18 4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,
19 4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,
20 4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,
21 4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,
22 4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
23 4-phenylmethylamino-6-methanesulfonylamino-2-(3-pyridyl)quinazoline,
24 4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,
25 4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,
26 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
27 4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
28 4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
29 4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,
30 4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,
31 4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
32 4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,
33 4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,
34 4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,
35 4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,
36 4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,

37 4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,
38 4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,
39 4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,
40 4-phenylmethylamino-6-acetylamino-2-(4-pyridyl)quinazoline,
41 4-phenylmethylamino-6-methanesulfonylamino-2-(4-pyridyl)quinazoline,
42 4-phenylmethylamino-6-sulfamoyl-2-(4-pyridyl)quinazoline,
43 4-phenylmethylamino-6-acetoxy-2-(4-pyridyl)quinazoline,
44 4-phenylmethylamino-6-chloro-2-(4-pyridyl)quinazoline,
45 4-phenylmethylamino-6-bromo-2-(4-pyridyl)quinazoline,
46 4-phenylmethylamino-7-fluoro-2-(4-pyridyl)quinazoline,
47 4-phenylmethylamino-6-trifluoromethyl-2-(4-pyridyl)quinazoline,
48 4-phenylmethylamino-6-hydroxy-2-(4-pyridyl)quinazoline,
49 4-phenylmethylamino-6-nitro-2-(4-pyridyl)quinazoline,
50 4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,
51 4-phenylmethylamino-6-methyl-2-(1-imidazolyl)quinazoline,
52 4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,
53 4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline
54 4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,
55 4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
56 4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,
57 4-phenylmethylamino-6-(N',N-dimethylamino)-2-(1-imidazolyl)quinazoline,
58 4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,
59 4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,
60 4-phenylmethylamino-6-sulfamoyl-2-(1-imidazolyl)quinazoline,
61 4-phenylmethylamino-6-acetoxy-2-(1-imidazolyl)quinazoline,
62 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,
63 4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,
64 4-phenylmethylamino-7-fluoro-2-(1-imidazolyl)quinazoline,
65 4-phenylmethylamino-6-trifluoromethyl-2-(1-imidazolyl)quinazoline,
66 4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,
67 4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,
68 4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,
69 4-phenylamino-2-(3-pyridyl)quinazoline,
70 4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
71 4-phenethylamino-2-(3-pyridyl)quinazoline,
72 4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
73 4-(cyclohexylmethyl)amino-2-(3-pyridyl)quinazoline,
74 4-(2-azepinylmethyl)amino-2-(3-pyridyl)quinazoline,
75 4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
76 4-((1-methyl-2-pyrrolyl)methyl)amino-2-(3-pyridyl)quinazoline,
77 4-(3-isoxazolyl)amino-2-(3-pyridyl)quinazoline,
78 4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,
79 4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,
80 4-phenylmethylamino-2-(2-azepinyl)quinazoline,
81 4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,
82 4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,
83 4-phenylmethylamino-2-(2-triazinyl)quinazoline,
84 4-phenylmethylamino-2-(2-pyridyl)quinazoline,
85 4-phenylmethylamino-2-(4-pyridyl)quinazoline,
86 4-phenylmethylamino-2-(2-(3-pyridyl)ethyl)quinazoline,
87 4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,
88 4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,
89 4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
90 4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,
91 4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline,
92 4-phenylmethylamino-2-(1-triazolyl)quinazoline,
93 4-phenylmethylamino-2-(2-thienyl)quinazoline,
94 4-phenylmethylamino-2-(2-furyl)quinazoline,

95 6-methyl-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline
96 6,7-dimethoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline
97 6-acetyloxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,
98 6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,
99 6-bromo-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,
100 6-iodo-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
101 7-fluoro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
102 6-hydroxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)-quinazoline,
103 6-nitro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
104 6-methyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
105 6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
106 6-acetyloxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
107 6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
108 6-bromo-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
109 6-iodo-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
110 7-fluoro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
111 6-hydroxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
112 6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
113 6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
114 6-methyl-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
115 6-methoxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
116 6,7-dimethoxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)-quinazoline,
117 6-acetyloxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
118 6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
119 6-bromo-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
120 6-iodo-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
121 7-fluoro-4-(2-dimethylaminoethyl)amino-2-(1 -imidazolyl)quinazoline,
122 6-hydroxy-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
123 6-nitro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
124 6-methyl-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
125 6-methoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
126 6,7-dimethoxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
127 6-acetyloxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
128 6-chloro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
129 6-bromo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
130 6-iodo-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
131 7-fluoro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
132 6-hydroxy-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
133 6-nitro-4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
134 6-methyl-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
135 6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
136 6,7-dimethoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
137 6-acetyloxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
138 6-bromo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
139 6-iodo-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
140 7-fluoro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
141 6-hydroxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
142 6-nitro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,

and further those described in Examples below are also representative compounds of the present invention.

Salts and Acid addition salts

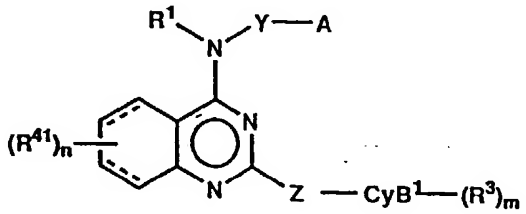
The compounds of the formula (I), if desired, may be converted into acid addition salts by known methods. Preferably, acid addition salts are non-toxic and water-soluble. The suitable acid addition salts are, for example, salts of an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, or an organic acid such as acetic acid, lactic acid, tartaric acid, benzoic acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

The compounds of the formula (I), if desired, may be converted into salts by known methods. Preferable, salts are non-toxic salts and water-soluble. The suitable salts are salts of alkaline metal (sodium, potassium etc.), salts of alkaline earth metal (calcium, magnesium etc.), ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, phenylmethylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine etc.).

Throughout the specification including claims, it may be easily understood by those skilled in the art, that the alkyl, alkoxy, groups include straight- chained and also branched-chained ones. Accordingly, all isomers produced by the difference in stereo configuration, such as asymmetric carbons are included in the present invention.

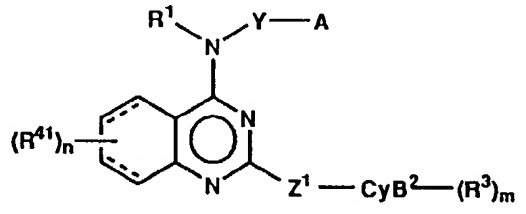
Preparations

According to the present invention, of the compounds of the present invention, the compounds of the formula:



(IA)

wherein R^{41} is (1) hydrogen, (2) C1-4 alkyl, (3) C1-4 alkoxy, (4) -$COOR^8$, (5) -NR^9R^{10}, in which R^9 and R^{10} are as hereinbefore defined, provided that both R^9 and R^{10} are not hydrogen, (6) $SO_2NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1-4 alkylthio, (12) tri(C_{1-4} alkyl)silylethynyl, (13) -SO_2N = $CHNR^{12}R^{13}$, in which R^{12} and R^{13} are as hereinbefore defined, or (14) -$CONR^{14}R^{15}$, in which R^{14} and$R^{15}$are as hereinbefore defined, CyB^1 is as hereinbefore defined for CyB, provided that a carbon atom in the ring should bond to Z, and the other symbols are as hereinbefore defined; and the compounds of the formula:

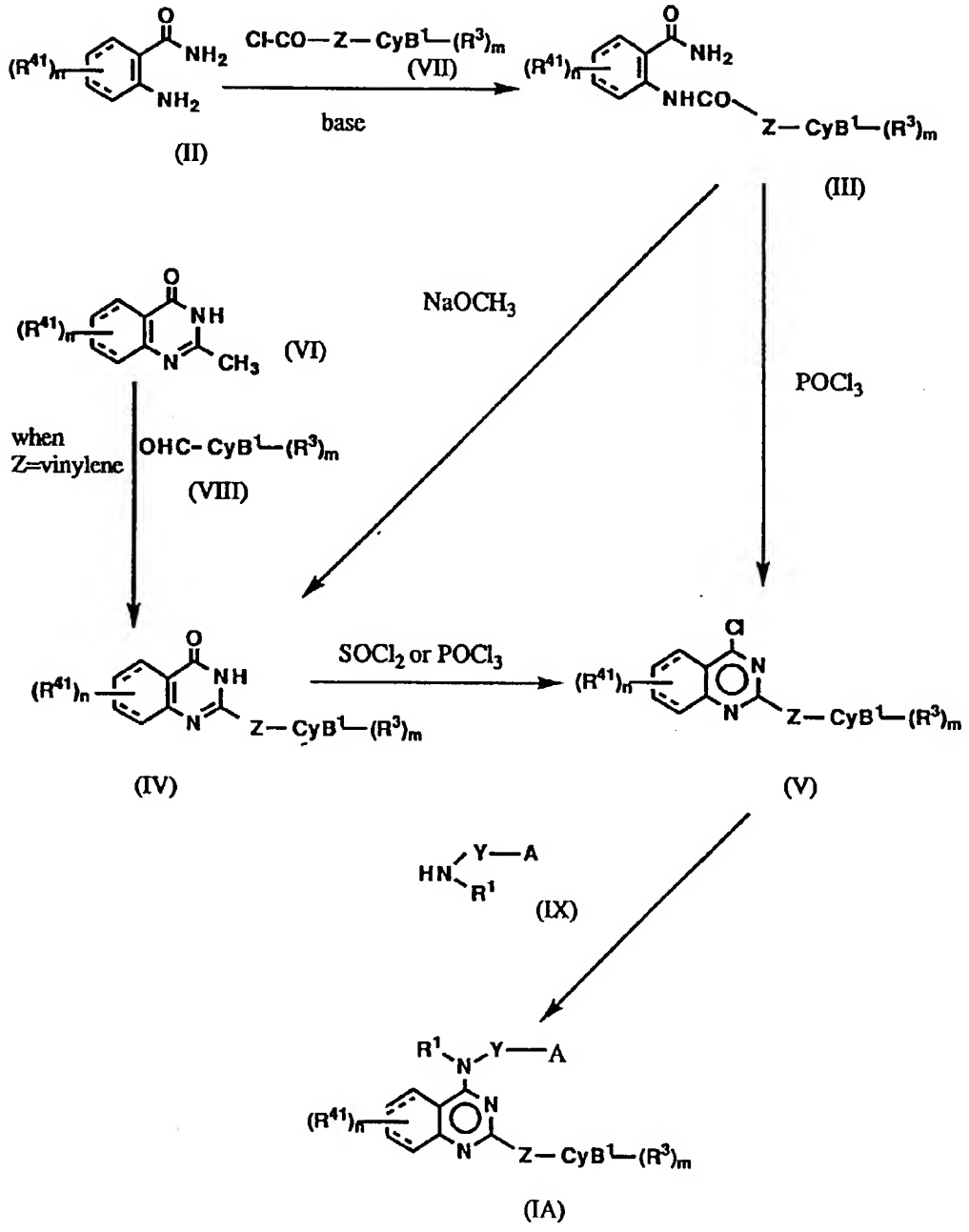


(IB)

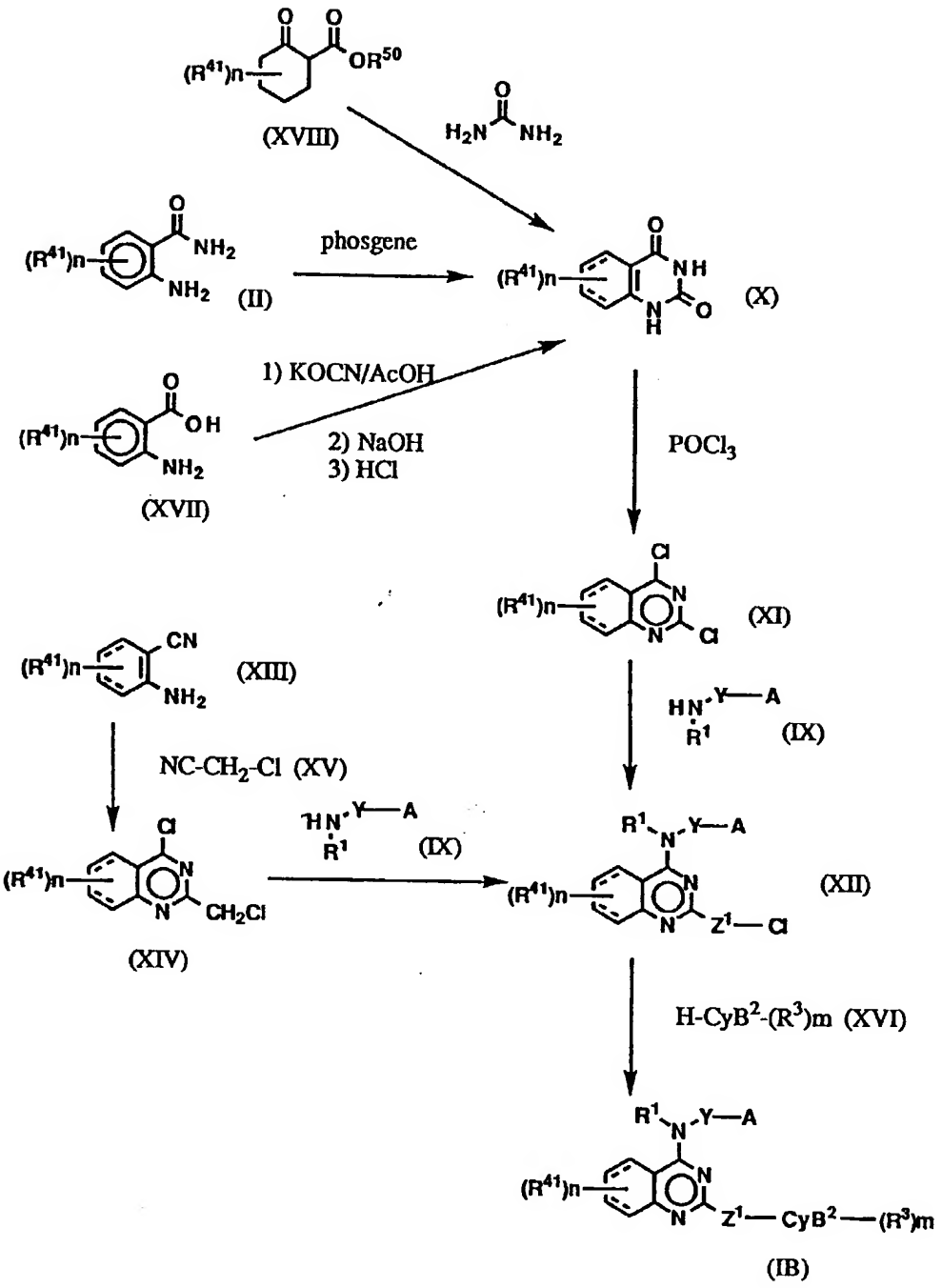
wherein Z^1 is single bond or methylene, CyB^2 is as hereinbefore defined for CyB, provided that a nitrogen atom in the ring should bond to Z^1,

and the other symbols are as hereinbefore defined; may be prepared by using a series of reactions depicted in Scheme A and B, respectively, wherein R^{50} is C_{1-4} alkyl and the other symbols are as hereinbefore defined.

Scheme A


Cl-CO—Z—CyB1—(R3)m
(VII)
base
(II)
(III)
NaOCH3
POCl3
(VI)
when Z=vinylene
OHC-CyB1—(R3)m
(VIII)
SOCl2 or POCl3
(IV)
(V)
(IX)
(IA)

Scheme B



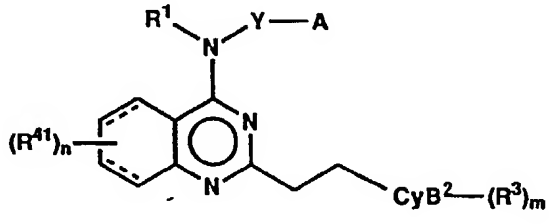
Each reaction in Scheme A and B may be carried out by methods known per se, under conditions described therein.

For example, the compounds of the formula (IA) may be prepared from those of the formula (V) by the reaction with an amine of the formula (IX) in a proper organic solvent such as a lower alkanol (e.g. ethanol) or tetrahydrofuran, or a mixture thereof, at a temperature from ambient to reflux, for several hours to several

days, if necessary in the presence of a base such as triethylamine.

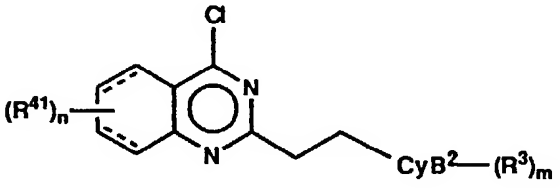
Further, the compounds of the formula (IB) may be prepared from those of the formula (XII) by the reaction with a cyclic amine of the formula (XVI) in phenol at a reflux temperature for several hours.

Furthermore, the compounds of the present invention, of the formula:



(IC)

wherein the various symbols are as hereinbefore defined; may be prepared from those of the formula:



(XIX)

wherein the various symbols are as hereinbefore defined; by the methods described hereinbefore for the conversion of the compounds of the formula (V) into those of the formula (IA). The compounds of the formula (XIX) may be prepared by the methods similar to those described hereinbefore in Scheme A.

On the other hand, the compounds of the formula (I) other than those of the formulae (IA), (IB) and (IC) may be prepared by the methods known per se described below.

The compounds of the formula (I) wherein R^4 is amino may be prepared from those wherein R^4 is nitro, by the reduction with zinc etc. in a proper organic solvent.

The compounds of the formula (I) wherein R^4 is hydroxy may be prepared from those wherein R^4 is alkoxy such as methoxy, by the reaction with hydrogen bromide or tribromoboron.

The compounds of the formula (I) wherein R^4 is -NHCOR^{11}, wherein R^{11} is as hereinbefore defined, may be prepared from those wherein R^4 is nitro, by the reaction with the corresponding organic acid such as acetic acid in the presence of zinc dust.

The compounds of the formula (I) wherein R^4 is $NHSO_2R^{11}$, wherein R^{11} is as hereinbefore defined, may be prepared from those wherein R4 is amino by the reaction with the corresponding alkylsulfonyl chloride such as methanesulfonyl chloride.

The compounds of the formula (I) wherein R^4 is -OCOR^{11}, wherein R^{11} is as hereinbefore defined, may be prepared from those wherein R^4 is hydroxy by the esterification with the corresponding organic acid such as acetic acid.

The compounds of the formula (I) wherein R^4 is C1-4 alkylsulfinyl or C1-4 alkylsulfonyl may be prepared from those wherein R^4 is C1-4 alkylthio by the oxidation by oxidating agent such as hydrogen peroxide.

The compounds of the formula (I) wherein R^4 is hydroxymethyl may be prepared from those wherein R^4 is alkyoxycarbonyl, by the reduction with reducing agent such as lithium borohydride, lithium aluminum hydride etc.

The compounds of the formula (I) wherein R^4 is ethynyl may be prepared from those wherein R^4 is tri(C1-4 alkyl)silylethynyl, by the removal reaction of silyl group with tetrabutylammonium halide.

The compounds of the formula (I) wherein R^4 is acetyl may be prepared from those wherein R^4 is ethynyl, by the reaction with mercury sulfate and acetic acid in an acidic condition.

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

The starting materials of the formulae (II), (VI) and (XIII), and each reagents of the formulae (VII), (VIII),

(IX), (XV), (XVI), (XVII) and (XVIII) used in the process for the preparation of the present invention are known per se or may be easily prepared by known methods.

Effect

The compounds of the formula (I), pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof, of the present invention have an inhibitory effect on cGMP-PDE, or additionally on TXA_2 synthetase, and are, therefore, useful for the prevention and/or treatment of not only diseases induced by enhancement of the metabolism of cGMP, such as hypertension, heart failure, myocardial infarction, angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, but also diseases induced by enhancement of the synthesis of TXA_2 such as inflammation, thrombosis, cerebral apoplexy, asthma, cardiostenosis, cerebral infarction etc, in mammals, especially in humans.

Especially, it is very useful for the prevention and/or treatment of heart failure, angina pectoris, pulmonary hypertension, various kinds of renal diseases, hyoiuresis induced by heart failure.

The inhibitory effect on cGMP-PDE and TXA_2 synthetase, of the compounds of the present invention were confirmed by screening tests as described below.

(1) Inhibitory effect on cGMP-PDE

Method

PDE IC was isolated from human platelets according to standard methods previously described in Lugnier, C. et al.,*Biochem. Pharmacol.* **35**: 1743, 1986 (incorporated in its entirety by reference). Typically, connective tissue and adventitia were removed and 1-2 units of platelets were suspended in 10 volumes of buffer A (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and 5 mM Na2EDTA) using a Brinkman polytron. The proteinase inhibitors leupeptin, pepstatin A, and phenylmethyl-sulfonyl fluoride (PMSF) were also included in this buffer (final concentration of 100 nM each). The homogenate was centrifuged at 100,000g for 60 minutes. The supernatant was then removed and filtered through four layers of cheesecloth. The supernatant was applied to a DWAE-Trisacryl M column. The column was washed with several bed volumes of buffer B (20 mM Tris-HCl, pH 7.5, containing 2 mM magnesium acetate, 1 mM dithiothreitol, and proteinase inhibitors) and eluted by two successive linear NaCl gradients (0.05-0.15 M, 300 ml total; 0.15-0.40 M, 200 ml total). Five milliliterfractions were collected and assayed for cyclic GMP PDE activity.

Phosphodiesterase activity was measured, as described by Thompson, et al., *Adv. Cyclic Nucleotide Res.* **10**: 69, 1979 (incorporated in its entirety by reference), in a reaction medium containing 40 mM Tris-HCl (pH 8.0), 5 mM MgCl2, and 1 mM dithiothreitol. The concentration of substrate (^{3}H-cGMP) was 0.2mM. Compounds of the present invention were dissolved in dimethyl sulfoxide (DMSO) at a final concentration of 2.5%. This concentration of DMSO inhibited enzyme activity by approximately 10%. The IC_{50} values (concentration that produced 50% inhibition of substrate hydrolysis) for the compounds examined were determined from concentration-response curves in which concentrations typically ranged from 10^{-8} to 10^{-3} M for the less potent inhibitors (half-log increments).

Result

The result is shown in Table 1 below.

Table 1 : Inhibitory activity on cGMP-PDE

Compounds Example No.		Inhibitory activity IC_{50}, (M)
3 (e)	(free base)	4.5×10^{-7}
3 (i)	(2HCl)	3.6×10^{-7}
3 (ee)	(2HCl)	3.0×10^{-7}
3 (k)	(3HCl)	2.8×10^{-6}
7	(free base)	2.0×10^{-7}
5	(free base)	2.6×10^{-7}
3 (t)	(free base)	7.2×10^{-7}
3(l)	(2HCl)	7.6×10^{-7}
6 (b)	(2HCl)	3.0×10^{-6}
6 (a)	(2HCl)	2.8×10^{-9}
3 (a)	(2HCl)	1.05×10^{-7}
3 (z)	(2HCl)	1.0×10^{-8}
3(ff)	(2HCl)	4.2×10^{-9}
6(c)	(2HCl)	2.3×10^{-9}
6(k)	(2HCl)	6.3×10^{-7}
6(l)	(free base)	2.15×10^{-7}
6(o)	(2HCl)	1.3×10^{-7}
8	(2HCl)	8.9×10^{-7}
6(x)	(2HCl)	2.7×10^{-7}
11(a)	(2HCl)	8.7×10^{-7}
11(d)	(HCl)	4.7×10^{-8}
11(e)	(2HCl)	5.5×10^{-7}

(2) Inhibitory effect on TXA_2 synthetase

Method

Male Wistar rats were starved overnight. Five hundreds microliter of heparinized (10U/mL) whole blood was collected from abdominal aorta using polyethylene syringe (needle: 22 or 26G). The blood freshly drawn from animal was preincubated with 5 μL of test compound at 37 °C. Five minutes later, 2.5 μL of 6 mM of Ca ionophore A23187 (final concentration of 30 μM) was added into tube, and incubation mixture was further incubated for 15 min. The reaction was terminated by centrifugation of tubes at 12,000 rpm for 2 min. TXB_2 content in the supernatant was determined by EIA as follows.

One milliliter of 0.5 M glycine-HCl buffer (pH 3.2) was added to 100 μL of sample. The samples were mixed well and centrifuged at 1,700 G for 10 min at 4 °C. The extracted supernatant was applied to a SEP-PAK (registered Trade Mark) C_{18} cartridge (Waters Assoc.). After washing with 10 mL of distilled water followed by 10 mL each of 15% ethanol and petroleum ether, the sample was eluted with 3 mL of ethyl acetate. The ethyl acetate fraction was evaporated to dryness under gentle N_2 stream and the residue was dissolved in EIA buffer

(final volume of 1 mL) following the addition of 300 µL of 0.01 M $NaHCO_3$-NaOH buffer (pH 10.0). EIA for TXB_2 was carried out according to a legend attached to the kit (Chyman Chemical Co., Inc.). Overall recovery of TXB_2 in this extraction procedure was 90%. The IC_{50} values (concentration that produced 50% inhibition of TXB_2 synthesis) for the compounds examined were determined from concentration-response curves.

Result

Table 2: Inhibitory activity on TXA_2 synthetase

Compounds Example No.		Inhibitory activity IC_{50}, (M)
3 (e)	(free base)	5.8×10^{-6}
5	(free base)	2.2×10^{-7}
11(e)	(2HCl salt)	1.77×10^{-6}
6(bb)	(2HCl salt)	2.0×10^{-7}
6(kk)	(2HCl salt)	3.6×10^{-6}
6(nn)	(2HCl salt)	1.35×10^{-6}
18(a)	(2HCl salt)	1.33×10^{-6}

On the other hand, it was confirmed that the acute toxicity of the compound of the present invention is very weak. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

Application for Pharmaceuticals

For the purpose above described, the compounds, of the formula (I), of the present invention, pharmaceutically acceptable salts and acid addition salts thereof and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hrs. per day intravenously.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

Administration of the compounds of the present invention, may be as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, micro crystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.) The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate etc.), stabilizing agents (such as lactose etc.), and assisting agents for dissolving (such as glutamic acid, aspartic acid etc.).

The tablets or pills may, if desired, be coated with film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

In such compositions, one or more of the active compound(s) is or are comprise in inert diluent(s) commonly used in the art (purified water, ethanol etc.).

Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents etc.), sweetening agents, flavouring agents, perfuming agents and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid etc.)

For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one more of active compound(s) is or are admixed with at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE80 (registered trade mark) etc.).

Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, aspartic acid etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions, for example, by freeze- drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

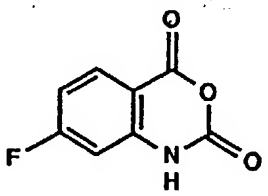
Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

Reference example and Examples

The following Reference examples and examples are intended to illustrate, but not limit, the present invention. In Reference examples and examples, "mp" shows "melting point".

Reference example 1

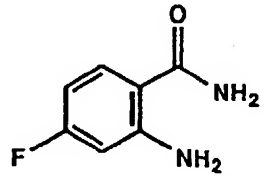
4-fluoroisatoic anhydride



To a solution of 2-amino-4-fluorobenzoic acid (4.65 g) in 50 mL of mixed solvent (10 : 1 = toluene : tetrahydrofuran) was added phosgene (4.46 g, 1.93 M solution of toluene) dropwise via a drop funnel. The mixture was stirred at room temperature for 1 hour and then heated to reflux over night. The mixture was concentrated to about 10 mL and cooled in refrigerator. The precipitate was filtered, washed with ether (5 mL X 2) and air-dried to give the title compound (5.43 g) as a white solid having the following physical data.
NMR (200MHz, DMSO-d6): δ 6.92 (dd, 1H), 7.11 (td, 1H), 8.00 (dd, 1H), 11.92 (broad, 1H).

Reference example 2

4-fluoroanthranilamide



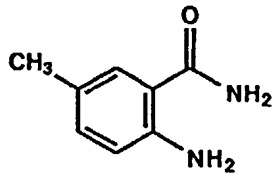
A solution of the isatoic anhydride compound (3.62 g, prepared in Reference example 1) in 100 mL of tetrahydrofuran was placed in a 200 mL round bottle equipped with gas in- and outlet. The anhydrous ammonia gas was gently bubbled into the solution for 1.5 to 2 hours. After removal of the solvent the residue was taken up in methylene chloride (30 mL) and water (30 mL). The precipitate was collected by filtration and washed with methylene chloride (10 mL) to give the title compound (1.95 g) as a pale white solid having the following physical data.

NMR (200MHz, DMSO-d6): δ 6.70 (m, 1H), 6.82 (m, 1H), 6.90 (broad, 2H), 7.72 (m, 1H).

The following compounds were obtained by the same procedure as Reference example 1 and Reference example 2, by using the corresponding substituted anthranilic acid compound.

Reference example 2(a)

5-methylanthranilamide

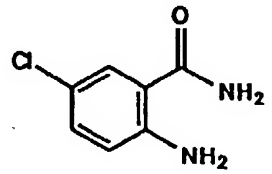


The product was collected by filtration as a pale solid.

NMR (200MHz, DMSO-d6): δ 2.24 (s, 3H), 5.50 (broad, 2H), 6.62 (d, 1H), 7.07 (dd, 1H), 7.16 (d, 1H).

Reference example 2(b)

5-chloroanthranilamide

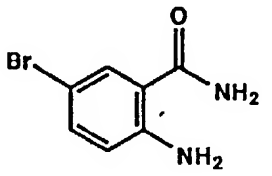


The product was collected by filtration as a pale solid.

NMR (200MHz, DMSO-d6): δ 5.68 (broad, 2H), 6.64 (d, 1H), 7.20 (dd, 1H), 7.35 (d, 1H).

Reference example 2(c)

5-bromoanthranilamide

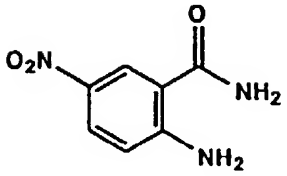


The product was collected by filtration as a pale brown.

NMR (200MHz, DMSO-d6): δ 6.66 (dd,1H) 6.72 (broad, 2H), 7.20 (broad, 1H), 7.26 (dt, 1H), 7.70 (t, 1H), 7.82 (broad, 1H).

Reference example 2(d)

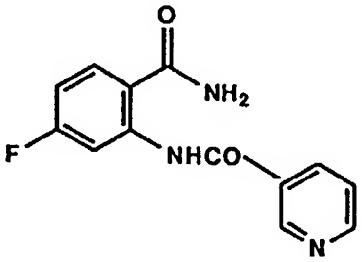
5-nitroanthranilamide



The product was collected by filtration as a solid.
NMR (200MHz, DMSO-d6): δ 6.80 (dd,1H) 7.40 (broad, 1H), 7.90 (broad, 2H), 8.03 (dt, 1H), 8.20 (broad, 1H), 8.56 (t, 1H).

Reference example 3

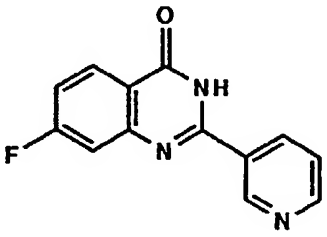
4-fluoro-2-[N-(3-pyridylcarbonyl)amino]benzamide



To a solution of the anthranilamide compound (1.54 g, prepared in Reference example 2) and triethylamine (1.4 g) in 100 mL of tetrahydrofuran was added nicotinoyl chloride hydrochloride (1.95 g). The resulting mixture was heated to reflux for one to three days and then concentrated. The residue was taken up in water (25 mL) and chloroform (30 mL). The insoluble crude product was collected by filtration and then vacuum dried. The crude product was triturated with 10 mL of ether and pentane solution (1:1) to afford the title compound (2.27 g) as a white solid having the following physical data.
NMR (200MHz, DMSO-d6): δ 7.10 (td, 1H), 7.80 (m, 1H), 7.99 (broad, 1H), 8.07 (m, 1H), 8.40-8.55 (m, 3H), 8.90 (m, 1H), 9.15 (m, 1H).

Reference example 4

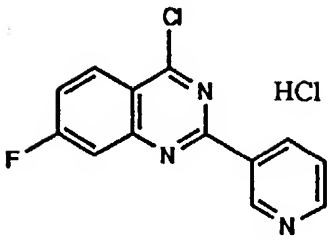
7-fluoro-2-(3-pyridyl)quinazolin-4-one



To a suspension of the benzamide compound (1.6 g, prepared in Reference example 3) in 60 mL of toluene was added sodium methoxide (853 mg). The solution was heated to reflux for one to three days. After cooling to room temperature, the mixture was quenched with ammonium chloride solution (30 mL) with a vigorously shaking. The mixture was cooled in refrigerator and the insoluble product was collected by filtration and dried in vacuum to give the title compound (1.39 g) as a white solid having the following physical data.
NMR (200MHz, DMSO-d6): δ 7.43 (td, 1H), 7.53-7.64 (m, 2H), 8.20-8.28 (m, 1H), 8.50 (dt, 1H), 8.78 (dd, 1H), 9.29 (m, 1H).

Reference example 5

4-chloro-7-fluoro-2-(3-pyridyl)quinazoline hydrochloride

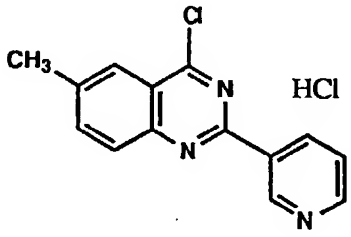


A suspension of the quinazolinone compound (1.2 g, prepared in Reference example 4) in 20 mL of thionyl chloride was heated to reflux for three hours. The excess of thionyl chloride was removed by distillation. The residue was distilled azeotropically with benzene (5 mL X 3) and then reduced the total volume to about 5 mL. After cooling in refrigerator, precipitate was collected by filtration and washed with benzene twice to give the title compound (1.38 g) as a crystalline solid having the following physical data.
NMR (200MHz, DMSO-d6): δ 7.80-7.95 (m, 2H), 8.07 (dd, 1H), 8.43-8.49 (m, 1H), 8.95 (d, 1H), 9.06 (dt, 1H), 9.65 (m, 1H).

The following compounds were obtained by the same procedure as Reference example 3→ Reference example 4→ Reference example 5, by using the anthranilamide compound prepared in Reference example 2(a), 2(b) or 2(c), or being on sale, and the corresponding acid chloride.

Reference example 5(a)

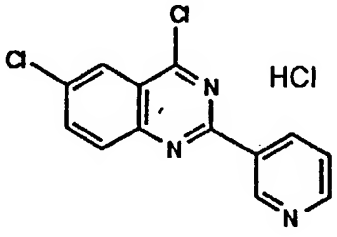
4-chloro-6-methyl-2-(3-pyridyl)quinazoline hydrochloride



The product was collected by filtration as a white solid.
NMR (200MHz, DMSO-d6): δ 2.62 (s, 3H), 7.96-8.14 (m, 4H), 8.98 (d, 1H), 9.16 (d, 1H), 9.63 (m, 1H).

Reference example 5(b)

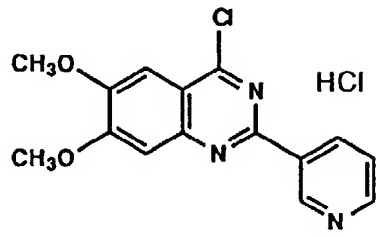
4,6-dichloro-2-(3-pyridyl)quinazoline hydrochloride



The product was collected by filtration as a white solid.
mp : 210-214 °C.
NMR ($CDCl_3$): δ 7.28-8.17 (m, 3H), 8.35 (m, 1H), 8.89 (dd, 1H), 9.55 (dt, 1H), 9.98 (d, 1H).

Reference example 5(c)

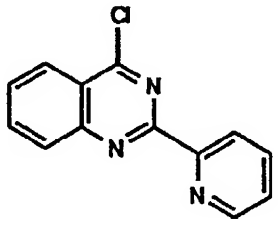
4-chloro-6,7-dimethoxy-2-(3-pyridyl)quinazoline hydrochloride



The product was collected by filtration as a white solid.
NMR (200MHz, DMSO-d6): δ 4.04 (s, 3H), 4.06 (s, 3H), 7.46 (s, 1H), 7.56 (s, 1H), 7.95 (m, 1H), 8.93 (d, 1H), 9.09 (d, 1H), 9.60 (m, 1H).

Reference example 5(d)

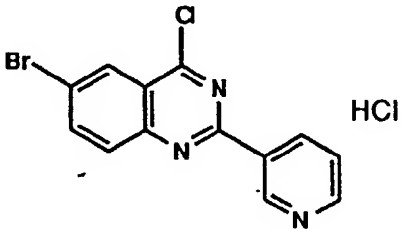
4-chloro-2-(2-pyridyl)quinazoline



The product was collected by filtration as a light brown powder.
mp : 120-121 °C

Reference example 5(e)

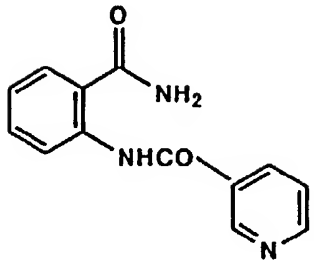
6-bromo-4-chloro-2-(3-pyridyl)quinazoline hydrochloride



NMR (200MHz, DMSO-d6): δ 8.02 (m, 1H) 8.14 (dd, 1H), 8.33 (dt, 1H), 8.50 (t, 1H), 9,01 (d, 1H), 9.14(d, 1H), 9.64 (t, 1H).

Reference example 6

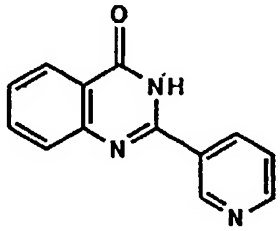
2-[N-(3-pyridylcarbonyl)amino]benzamide



To a solution of anthranilamide (8.2 g, being on sale) and triethylamine (18.0 g) in 100 mL of tetrahydrofuran/methylene chloride (1:1), was added nicotinoyl chloride hydrochloride (10.8 g). The mixture was allowed to stir at room temperature, under nitrogen atmosphere, for six hours. The solution was then concentrated under reduced pressure. The concentrate was taken up in ethyl acetate and water and the mixture filtered. The solid material was triturated in ether and filtered to give the title compound (11.5 g) as a yellow powder having the following physical data.
mp : 220-222 °C.

Reference example 7

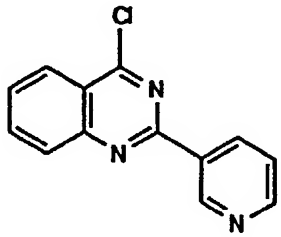
2-(3-pyridyl)quinazolin-4-one



To a solution of the benzamide compound (11.5 g, prepared in Reference example 6) in 100 mL of toluene was added 95% sodium methoxide (5.7 g). The solution was heated at 60-80° C for three hours under nitrogen atmosphere. After cooling to room temperature, the solution was diluted with ammonium chloride solution. After stirring for one-half hour, the mixture was filtered. An NMR of the filtered material indicated the reaction was incomplete. The material was taken up in toluene and ethanol and 95% sodium methoxide (5.7 g) was added. The resulting solution was heated to reflux and stirred via a mechanical stirrer, under nitrogen atmosphere, overnight. The solvent had evaporated and the concentrate in the flask was collected and washed with ammonium chloride solution and methylene chloride. The solid material was collected by filtration and allowed to dry to give the title compound as a gray powder having the following physical data.
mp : 275-276 °C.
NMR (200MHz, DMSO-d6): δ 7.50-7.61 (m, 2H), 7.75-7.90 (m, 2), 8.16 (d, 1H), 8.49 (m, 1H), 8.77 (d, 1H), 9.31 (s, 1H).
IR (KBr): ν 3185 (w), 3045 (m), 2915 (w), 1677 (s), 1603 (m), 1558 (w), 1474 (m), 769 (m) cm^{-1}.

Reference example 8

4-chloro-2-(3-pyridyl)quinazoline

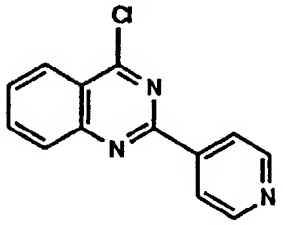


A solution of the quinazolinone compound (6.7 g, prepared in Reference example 7) and 5.7 mL of N,N-dimethylaniline in 200 mL of benzene was heated to reflux, under nitrogen atmosphere, for one-half hour with the removal of 15 mL of distillate. After cooling to room temperature, phosphorus oxychloride (4.5 g) was added and the resulting solution heated to reflux for six hours. After cooling to room temperature, the solution was washed with ice water and dilute sodium hydroxide solution. The organic extract was dried over sodium sulfate and concentrated under reduced pressure. The concentrate was triturated in ether and collected to give the title compound (3.0 g) having the following physical data.
mp : 178-179 °C.

The following compounds were obtained by the same procedure as Reference example 6→ Reference example 7→ Reference example 8, by using anthranilamide and the corresponding acid chloride.

Reference example 8(a)

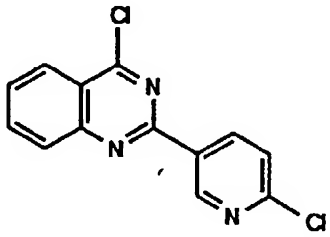
4-chloro-2-(4-pyridyl)quinazoline



The product was collected by filtration as a brown solid.
mp : 158-160 °C

Reference example 8(b)

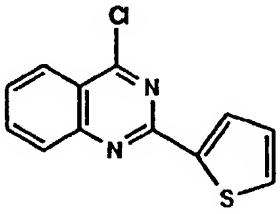
4-chloro-2-(2-chloro-5-pyridyl)quinazoline



NMR ($CDCl_3$): δ 7.47 (d, 1H), 7.73 (t, 1H), 7.95 (t, 1H), 8.05-8.32 (m, 2H), 8.81 (dd, 1H) 9.55 (ds, 1H).

Reference example 8(c)

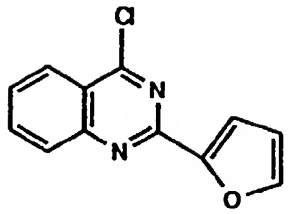
4-chloro-2-(2-thienyl)quinazoline



The product was collected by filtration as a tan powder.
mp : 121-124 °C

Reference example 8(d)

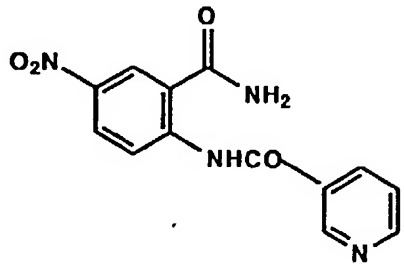
4-chloro-2-(2-furyl)quinazoline



The product was collected by the filtration as a tan powder.
mp : 116-119 °C

Reference example 9

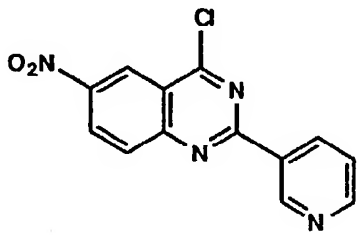
5-nitro-2-[N-(3-pyridylcarbonyl)amino]benzamide



The title compound was obtained by the same procedure as Reference example 3, by using 5-nitroanthranilamide (prepared in Reference example 2 (d)).
The product was collected by filtration as a white solid.
NMR (200MHz, DMSO-d6): δ 7.70 (m, 1H), 8.20 (broad, 1H), 8.35 (dt, 1H), 8.49 (dd, 1H), 8.85-8.92 (m, 3H), 9.15 (t, 1H).

Reference example 10

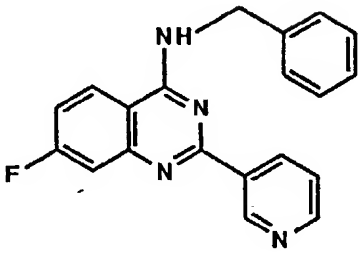
4-chloro-6-nitro-2-(3-pyridyl)quinazoline



A suspension of the benzamide compound (0.925 g, prepared in Reference example 9) in phosphorous oxychloride (6 mL) was heated to reflux for 16 hours. After cooling to room temperature, the mixture was diluted by chloroform (30 mL) and then poured into 30 mL of ice-water mixture. The mixture was cooled in ice bath and carefully neutralized to pH 8 with a temperature control under 10 °C. The aqueous layer was extracted with chloroform (50 mL X 3). Combined organic layers were dried over with potassium carbonate and concentrated under reduced pressure to give the title compound (0.8 g) having the following physical data.
NMR ($CDCl_3$): δ 7.27-7.35 (m, 2H), 7.52 (dd, 1H), 8.46-8.63 (m, 3H), 8.87 (d, 1H), 9.42 (s, 1H).

Example 1

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline



To a warm solution of the 4-chloroquinazoline compound (1.18 g, prepared in Reference example 5) in 50 mL ethanol was added phenylmethylamine (2.00 g). The mixture was heated to reflux for sixteen hours. The solution was then concentrated and the residue taken up in chloroform and ammonium chloride solution. The aqueous layer was extracted with chloroform (30 mL X 3) and dried over sodium sulfate. After concentration, the residue was triturated in pentane/ether solution to give the title compound (0.88 g) as a pale white solid having the following physical data.

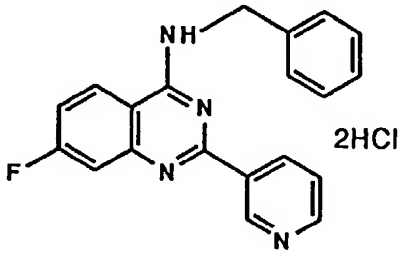
mp : 199-203 °C.

NMR ($CDCl_3$): δ 5.00 (d, 2H), 6.01 (broad, 1H), 7.20 (td, 1H), 7.25-7.50 (m, 6H), 7.55 (dd, 1H), 7.70-7.77 (m, 1H), 8.70 (dd, 1H), 8.79 (dt, 1H), 9.74 (m, 1H).

IR (KBr): ν 697 (s), 775 (s), 1166 (m), 1259 (m), 1341 (s), 1375 (s), 1444 (s), 1535 (s), 1592 (s), 1626 (s), 3135 (m), 3250 (m) cm^{-1}.

Example 2

4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline dihydrochloride



To a suspension of the free base (0.70 g, prepared in Example 1) in 10 ml methanol was added excess amount of HCl in methanol. The mixture was stirred at room temperature for a half of an hour. The solvent was removed and the residue was triturated in ether (30 ml). The title compound (0.84 g) as a white powder having the following physical data, was obtained after filtration.

mp : 250 °C.

NMR ($CDCl_3$): δ 4.50 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.64 (dt, 1H), 7.82 (dd, 1H), 7.99 (m, 1H), 8.67 (m,1H), 8.97 (dd, 1H), 9.15 (dd, 1H), 9.60 (d, 1H), 10.18 (broad, 1H).

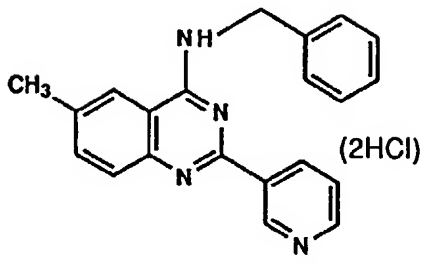
IR (KBr): ν 704 (m), 1266 (m), 1457 (s), 1574 (s), 1632 (s), 2920-2440 (broad, s), 3115 (broad, s) cm^{-1}.

Example 3

The following compounds were obtained by the same procedure as Example 1, or Example 1 and Example 2, by using the corresponding 4-chloroquinazoline compound prepared by Reference example 5, 5(a) to 5(e) or Reference example 8, 8(a) to 8(d) and the proper amine.

Example 3(a)

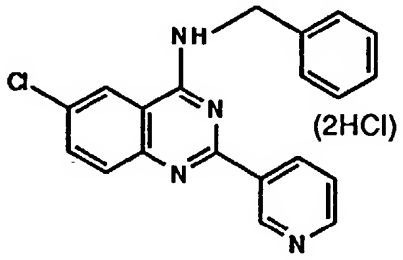
4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline and its salt



(free base)
The product was collected by filtration as a white solid.
mp : 179-180 °C (dec.).
NMR ($CDCl_3$): δ 5.03 (d, 2H), 5.97 (broad, 1H), 7.28-7.53 (m, 7H), 7.61 (dd, 1H), 7.86 (d, 1H), 8.69 (dd, 1H), 8.80 (dt, 1H), 9.76 (m, 1H).
IR (KBr): ν 699 (w), 1365 (m), 1407 (w), 1437 (w), 1535 (s), 1569 (s), 1591 (s), 3200 (m) cm^{-1}.
(2HCl salt)
The product was collected by filtration as a white powder.
mp : 265-269 °C (dec.).
NMR ($CDCl_3$): δ 2.50 (s, 3H), 5.03 (d, 2H), 7.28-7.42 (m, 3H), 7.48-7.53 (m, 2H), 7.80-7.91 (m, 2H), 8.06 (d, 1H), 8.45 (s, 1H), 8.91-9.00 (m, 2H), 9.55 (m, 1H).
IR (KBr): ν 704 (w), 1388 (m), 1568 (s), 1593 (s), 1617 (s), 2400-3100 (broad, s), 3200 (m), 3410 (broad, m) cm^{-1}.

Example 3(b)

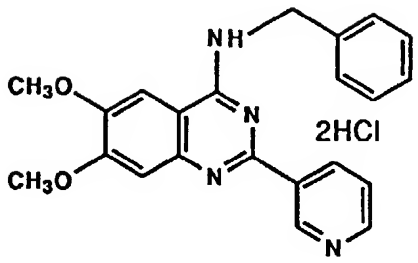
4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline and its salt



(free base)
The product was purified by column chromatography.
mp : 240 °C.
NMR ($CDCl_3$): δ 5.00 (d, 2H), 5.92 (broad, 1H), 7.32-7.51 (m, 6H), 7.71 (m, 2H), 7.90 (d, 1H), 8.71 (dd, 1H), 8.79 (dt, 1H), 9.75 (d, 1H).
IR (KBr): ν 697 (m), 1368 (s), 1419 (m), 1439 (m), 1534 (s), 1568 (s), 1590 (s), 3260 (w) cm^{-1}.
(2HCl salt)
The product was collected by filtration as a white powder.
mp : 255 °C (dec.).
NMR ($CDCl_3$): δ 4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.45-7.55 (m, 2H), 7.96-8.10 (m, 3H), 8.72 (m, 1H), 8.96 (d, 1H), 9.15 (d, 1H), 9.60 (m, 1H).
IR (KBr): ν 671 (w), 709 (m), 1356 (m), 1387 (s), 1457 (m), 1488 (m), 1518 (m), 1569 (s), 1608 (s), 1631 (s), 2335-2890 (broad, s), 3825 (s), 3230 (m), 3425 (m) cm^{-1}.

Example 3(c)

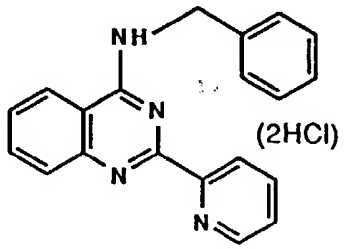
4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline and its salt



(free base)
The product was collected by filtration as a white solid.
mp : 193-196 °C.
NMR (200MHz, DMSO-d6): δ 3.92 (s, 3H), 3.94 (s, 3H), 4.92 (d, 2H), 6.90 (broad, 1H), 7.23-7.38 (m, 4H), 7.46-7.55 (m, 3H), 7.76 (s, 1H), 8.62-8.78 (m, 3H), 9.52 (m, 1H).
IR (KBr): ν 698 (m), 850 (m), 1026 (m), 1131 (m), 1183 (m), 1213 (s), 1243 (s), 1366 (s), 1450 (s), 1501 (s), 1528 (s), 1591 (s), 1622 (m), 3270 (w) cm^{-1}.
(2HCl salt)
The product was collected by filtration as a white solid.
mp : 240 °C (dec.).
NMR (200MHz, DMSO-d6): δ 3.98 (s, 6H), 5.01-5.06 (m, 2H), 7.25-7.41 (m, 3H), 7.74 (s, 1H), 7.85 (m, 1H), 8.14 (s, 1H), 8.90-8.95 (m, 2H), 9.56 (m, 1H).
IR (KBr): ν 1243 (w), 1287 (s), 1378 (m), 1473 (m), 1504 (s), 1542 (m), 1596 (m), 1634 (s), 2400-3200 (broad, s), 3440 (broad, s) cm^{-1}.

Example 3(d)

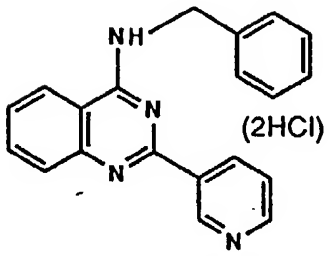
4-phenylmethylamino-2-(2-pyridyl)quinazoline and its salt



(free base):
The product was collected by filtration as a tan solid.
mp : 165-169 °C
(2HCl salt)
mp : 140-155 °C
NMR (200MHz, DMSO-d6): δ 5.12 (d, 2H), 7.35 (m, 3H), 7.58 (d, 2H), 7.83 (qd, 2H), 8.07 (t, 1H), 8.19-8.36 (m, 2H), 8.64 (d, 1H), 8.82 (d, 1H), 8.93 (d, 1H), 11.40 (t, 1H).
IR (KBr): ν 3370 (m), 3220 (m), 3200-2700 (m), 1625 (s), 1562 (s), 1524 (m), 1466 (m), 1385 (m), 765 (m) cm^{-1}.

Example 3(e)

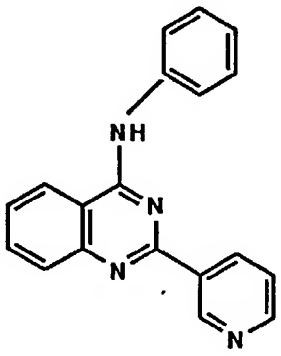
4-phenylmethylamino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 137-138 °C.
NMR ($CDCl_3$): δ 5.01 (d, 2H), 6.20 (t, 1H), 7.26-7.49 (m, 6H), 7.71-7.79 (t, 3H), 7.95 (d, 1H), 8.68 (bs, 1H), 8.82 (d, 1H), 9.75 (bs,1H).
IR (KBr): ν 3305 (m), 1584 (s), 1520 (s), 1437 (m), 1410 (m), 1365 (s), 1325 (w), 765 (m), 694 (m) cm^{-1}.
(2HCl salt)
mp : 225-235 °C
NMR (200MHz, DMSO-d6): δ 5.05 (d, 2H), 7.22-7.43 (m, 3H), 7.52 (m, 2H), 7.78 (t, 1H), 7.94-8.13 (m, 2H), 8.36 (s, 1H), 8.78 (d, 1H), 9.00 (dd, 1H), 9.12 (dd, 1H), 9.70 (s, 1H), 11.16 (broad t, 1H).
IR (KBr): ν 3300-2615 (broad,s), 1629 (s), 1605 (s), 1569 (s), 1456 (m), 1384 (m), 763 (m), 705 (m) cm^{-1}.

Example 3(f)

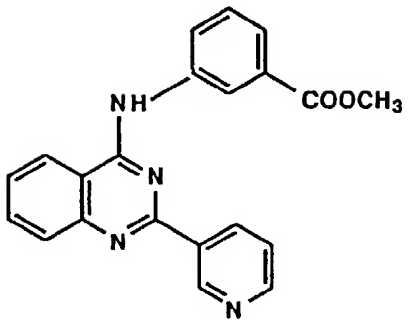
4-phenylamino-2-(3-pyridyl)quinazoline



The product was collected by filtration as a yellow powder.
mp :173-178 °C.
NMR (200MHz, DMSO-d6): δ 7.29 (t, 1H), 7.53 (t, 2H), 7.72-8.17 (m, 6H), 8.80 (d, 1H), 8.93 (d, 1H), 9.05 (d, 1H), 9.52 (s, 1H), 10.81 (bs, 1H).
IR (KBr): ν 3160 (bw), 1559 (s), 1520(s), 1411 (m), 1363 (m), 754 (m) cm^{-1}.

Example 3(g)

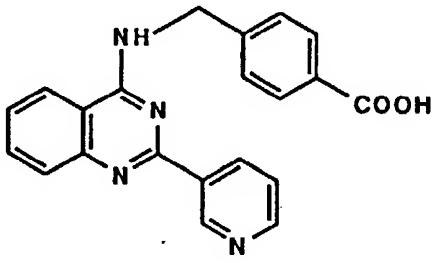
4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline



The product was collected by filtration as a yellow powder.
mp : 228-245 °C.
NMR (200MHz, DMSO-d6): δ 3.94 (s, 3H), 7.56-8.04 (m, 7H), 8.72-9.08 (m, 4H), 9.57 (s, 1H), 10.61 (bs, 1H).
IR (KBr): ν 3400 (bw), 1717(m), 1562 (s), 1520 (m), 1447 (m), 1374 (m), 1299 (m), 1278(m), 752 (m), 672 (w) cm^{-1}.

Example 3(h)

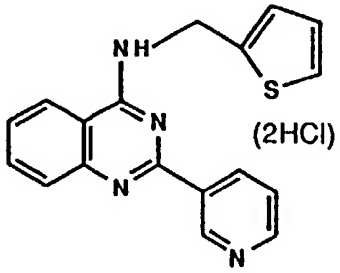
4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline



mp : 285-294 °C
NMR (200MHz, DMSO-d6): δ 4.98 (d, 2H), 7.50-7.62 (m, 4H), 7.81 (d, 2H), 7.90 (d, 2H), 8.37 (d, 1H), 8.65 (m, 2H), 9.13 (t, 1H), 9.49 (s, 1H).
IR (KBr): ν 3340 (broad), 1747 (m), 1586 (s), 1531 (s), 1366 (m), 765 (m) cm^{-1}.

Example 3(i)

4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

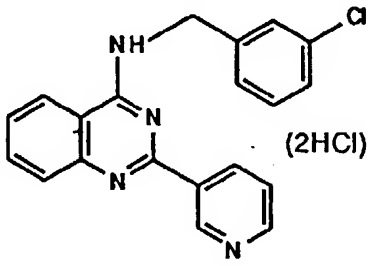


(free base)
mp : 195-197 °C
NMR (200MHz, DMSO-d6): δ 5.08 (d, 2H), 6.99 (m, 1H), 7.19 (m, 1H), 7.35 (dd, 1H), 7.55 (m, 2H), 8.30 (s, 1H), 8.69 (m, 1H), 8.83 (m, 1H), 9.13 (t, 1H).
IR (KBr): ν 3260 (bw), 1583 (s), 1525 (s), 1449 (m), 1359 (s), 763 (m), 747 (m), 720 (m) cm^{-1}.

(2HCl salt)
mp : 255 °C (dec.).
NMR (200MHz, DMSO-d6): δ 5.20 (d, 2H), 7.01 (m, 1H), 7.22 (m, 1H), 7.43 (s, 1H), 7.77 (t, 1H), 8.00 (m, 3H), 8.21 (d, 1H), 8.61 (d, 1H), 8.99 (d, 1H), 9.23 (d, 1H), 9.74 (s, 1H), 10.45 (bs, 1H).
IR (KBr): ν 3405 (w), 3060-2615 (broad, m), 2363 (w), 1631(s), 1608 (s), 1570 (s), 1458 (m), 1387 (m), 773 (m), 712 (m) cm^{-1}.

Example 3(j)

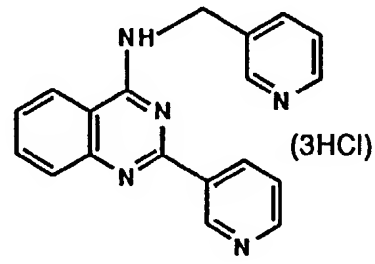
4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 203-205 °C
NMR (200MHz, DMSO-d6): δ 4.92 (d, 2H), 7.27-7.61 (m, 6H), 7.82 (d, 2H), 8.33 (d, 1H), 8.66 (m, 2H), 9.08 (t, 1H), 9.53 (s, 1H).
IR (KBr): ν 3245 (w), 3050-2800 (w), 1586 (s), 1533 (m), 1436 (w), 1412 (w), 1366 (m), 765 (w) cm^{-1}.
(2HCl salt)
mp : 235-250 °C
NMR (200MHz, DMSO-d6): δ 5.05 (d, 2H), 7.35 (m, 2H), 7.49 (m, 1H), 7.62 (s, 1H), 7.78 (t, 1H), 7.90-8.12 (m, 2H), 8.28 (s, 1H), 8.97 (m, 1H), 9.13 (dd, 1H), 9.66 (s, 1H), 10.97 (bs, 1H).
IR (KBr): ν 3035 (m), 2900-2700 (m), 1634 (m), 1610 (m), 1569 (m), 1387 (w), 780 (w), 710 (w) cm^{-1}.

Example 3(k)

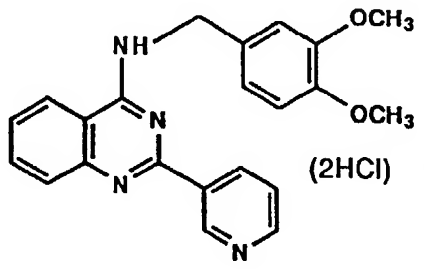
4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 157-161 °C
NMR (200MHz, DMSO-d6): δ 4.95 (d, 2H), 7.33 (m, 1H), 7.55 (m, 2H), 7.85 (m, 3H), 8.33 (d, 1H), 8.46 (dd, 1H), 8.65-8.76 (m, 3H), 9.10 (t, 1H), 9.57 (s, 1H).
IR (KBr): ν 3255 (m), 3050-2900 (w), 1586 (s), 1533 (s), 1438 (m), 1368 (s), 763 (m), 700 (m) cm^{-1}.
(3HCl salt)
mp : 240-257 °C
NMR (200MHz, DMSO-d6): δ 5.25 (d, 2H), 7.77 (t, 1H), 8.07 (m, 2H), 8.29 (d, 1H), 8.83 (m, 4H), 9.00 (d, 1H), 9.19 (m, 2H), 9.69 (s, 1H), 11.25 (bs, 1H).
IR (KBr): ν 3500 (w), 3100-2500 (broad, m), 1633 (s), 1611(s), 1569 (m), 1542 (m), 1457 (w), 790 (w), 720 (w) cm^{-1}.

Example 3(l)

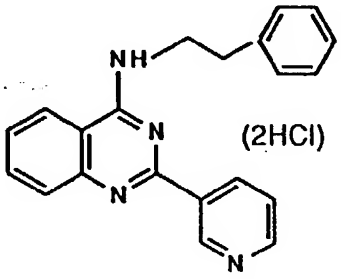
4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 155-159 °C
NMR (200MHz, DMSO-d6): δ 3.71 (d, 6H), 4.85 (d, 2H), 6.83-7.05 (m, 2H), 7.18 (s, 1H), 7.54 (m, 2H), 7.82 (d, 2H), 8.32 (d, 1H), 8.68 (dd, 1H), 8.77 (dd, 1H), 9.01 (t, 1H), 9.63 (s, 1H).
IR (KBr): ν 3395 (w), 3200-2900 (w), 1584 (s), 1514 (s), 1364 (m), 1263 (m), 1025 (m), 764 (w) cm^{-1}.
(2HCl salt)
mp : 215-220 °C
NMR (200MHz, DMSO-d6): δ 3.70 (s, 6H), 4.97 (d, 2H), 6.90 (d, 1H) 7.02 (d, 1H), 7.24 (s, 1H), 7.77 (t, 1H), 7.92 (m, 1H), 8.04 (t, 1H), 8.73 (d, 1H), 8.97 (d, 1H), 9.16 (dd,1H), 9.70 (s, 1H), 10.94 (bs, 1H).
IR (KBr): ν 3404 (m), 3200-2300 (m), 1631 (s), 1610 (s), 1569 (s), 1514 (s), 1264 (m), 765 (m) cm^{-1}.

Example 3(m)

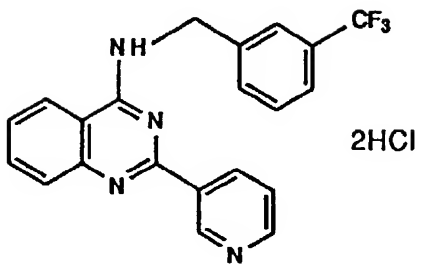
4-phenylethylamino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 136-139 °C
NMR (200MHz, DMSO-d6): δ 3.07 (t, 2H), 3.89 (q, 2H), 7.20-7.30 (m, 3H), 7.32 (d, 2H), 7.55 (m, 2H), 7.82 (s, 2H), 8.26 (s, 1H), 8.59 (t, 1H), 8.70 (m, 2H), 9.65 (s, 1H).
IR (KBr): ν 3290 (m), 3050-2900 (w), 1591 (s), 1514 (s), 1534 (s), 1442 (m), 1370 (s), 761 (m), 702 (m) cm^{-1}.
(2HCl salt)
mp : 220-250°C (dec.).
NMR (200MHz, DMSO-d6): δ 3.11 (t, 2H), 4.05 (q, 2H), 7.15-7.38 (m, 5H), 7.77 (t, 1H), 8.01 (m, 2H), 8.35 (d, 1H), 8.70 (d, 1H), 9.01 (d, 1H), 9.15 (d, 1H), 9.69 (s, 1H), 10.68 (bs, 1H).
IR (KBr): ν 3400 (w), 3100-2500 (m), 1633 (s), 1613 (s), 1570 (m), 1457 (m), 1385 (m), 790 (w), 720 (w) cm^{-1}.

Example 3(n)

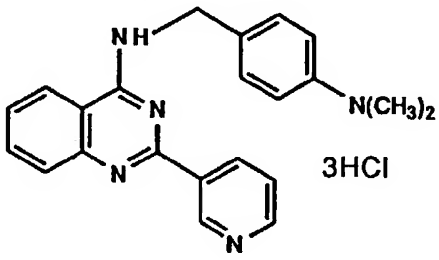
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline dihydrochloride



mp : >280 °C
NMR (200MHz, DMSO-d6): δ 5.14 (d, 2H), 7.52-8.35 (m, 8H), 8.70-9.20 (m, 3H), 9.67 (m, 1H).

Example 3(o)

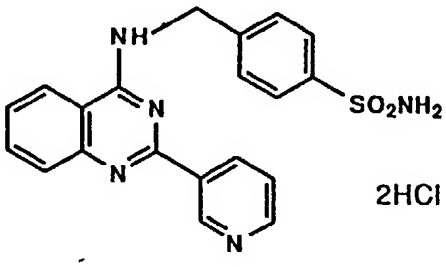
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline trihydrochloride



mp : 200-250 °C (dec.).
NMR (200MHz, DMSO-d6): δ 3.04 (s, 6H), 5.05 (d, 2H), 7.50-8.30 (m, 8H), 8.72 (s, 1H), 8.92-9.12 (m, 2H), 9.60 (m, 1H).

Example 3(p)

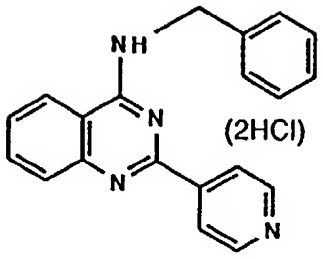
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline dihydrochloride



mp : 255-265 °C
NMR (200MHz, DMSO-d6): δ 5.10 (d, 2H), 7.32 (bs, 2H), 7.66-8.20 (m, 8H), 8.62 (d, 1H), 8.95 (m, 2H), 9.56 (ms, 1H).

Example 3(q)

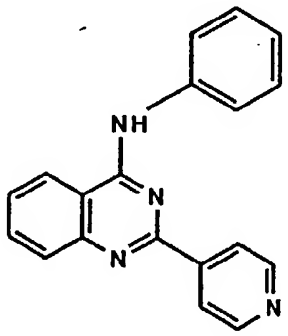
4-phenylmethylamino-2-(4-pyridyl)quinazoline and its salt



(free base)
mp : 195-197 °C
NMR (200MHz, DMSO-d6): δ 4.96 (d, 2H), 7.19-7.66 (m, 6H), 7.83 (d, 2H), 8.30 (d, 2H), 8.39 (d, 1H), 8.72 (d, 2H), 9.10 (t, 1H).
IR (KBr): ν 3250 (w), 1585 (s), 1561(s), 1529 (s), 1411 (m), 1374 (s), 1325 (s), 768 (m), 702 (m) cm^{-1}.
(2HCl salt):
mp : 260-270 °C
NMR (200MHz, DMSO-d6): δ 5.02 (d, 2H), 7.22-7.40 (m, 3H), 7.51 (d, 2H), 7.75 (t, 1H), 8.00 (t, 1H), 8.16 (d, 1H), 8.66 (d, 1H), 8.81 (d, 2H), 9.06 (d, 2H), 10.32 (bs, 1H).
IR (KBr): ν 3385 (m), 3210 (m), 3060-2600 (s), 1627 (s), 1604 (s), 1567 (s), 1505 (m), 1452 (m), 1383 (m), 760 (m), 709 (m) cm^{-1}.

Example 3(r)

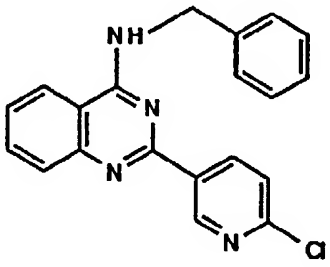
4-phenylamino-2-(4-pyridyl)quinazoline



mp : 270-274 °C
NMR (200MHz, DMSO-d6): δ 7.22 (t, 1H), 7.70 (m, 1H), 7.94 (m, 4H), 8.37 (m, 2H), 8.68 (d, 1H), 8.82 (d, 2H), 10.13 (s, 1H).
IR (KBr): ν 3270 (m), 3145 (m), 1620 (s), 1572 (s), 1524 (s), 1488 (s), 1443 (s), 1414 (s), 1374 (s), 749 (m), 702 (m) cm^{-1}.

Example 3(s)

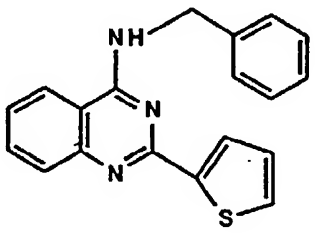
4-phenylmethylamino-2-(2-chloro-5-pyridyl)quinazoline



mp : 212-214 °C
NMR ($CDCl_3$): δ 4.96 (d, 2H), 6.03 (bs, 1H), 7.20-7.55 (m, 7H), 7.66-7.95 (m, 3H), 8.78 (m, 1H), 9.52 (m, 1H).
IR (KBr): ν 3315 (w), 1580 (s), 1532 (ms), 1446 (mw), 1343 (m), 1269 (w) cm^{-1}.

Example 3(t)

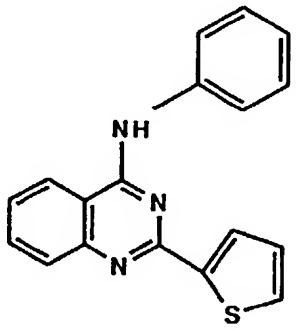
4-phenylmethylamino-2-(2-thienyl)quinazoline



mp : 158-163 °C
NMR (200MHz, DMSO-d6): δ 4.88 (d, 2H), 7.14-7.53 (m, 6H), 7.62-7.81 (m, 3H), 7.92 (m, 1H), 8.30 (d, 1H), 8.97 (t, 1H).
IR (KBr): ν 3305 (w), 1571 (s), 1519 (s), 1451(m), 1408 (m), 1377 (s), 769 (m), 730 (m), 737 (m) cm^{-1}.

Example 3(u)

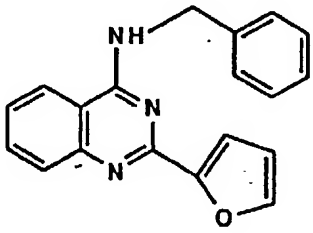
4-phenylamino-2-(2-thienyl)quinazoline



mp : 137-139 °C.
NMR (200MHz, DMSO-d6): δ 7.20 (m, 2H), 7.62-8.09 (m, 9H), 8.58 (d, 1H), 9.85 (s, 1H).
IR (KBr): ν 3430 (w), 1616 (w), 1662 (w), 1561 (s), 1461 (m), 1488 (m), 1461 (m), 1406 (m), 1374 (m), 749 (w) cm^{-1}.

Example 3(v)

4-phenylmethylamino-2-(2-furyl)quinazoline

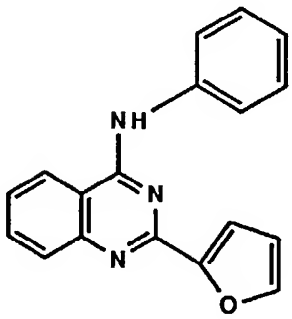


mp : 152-154 °C

NMR ($CDCl_3$): δ 4.95 (d, 2H), 6.00 (t, 1H), 6.56 (m, 1H), 7.31-7.49 (m, 7H), 7.62-7.76 (m, 3H), 7.97 (d, 1H).
IR (KBr): ν 3290 (m), 1589 (m), 1531 (s), 1365 (s), 1015 (m), 890 (m), 762 (s) cm^{-1}.

Example 3(w)

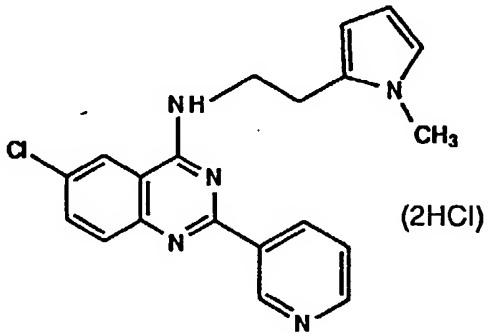
4-phenylamino-2-(2-furyl)quinazoline



mp :183-184 °C
NMR ($CDCl_3$): δ 6.58 (m, 1H), 7.13-737 (m, 2H), 7.39-7.58 (q, 4H), 7.65 (s, 1H), 7.72-7.94 (m, 4H), 8.03 (d, 1H).
IR (KBr): ν 3456 (w), 1607 (m), 1559 (s), 1524 (s), 1485 (s), 1446 (m), 1419 (m), 1360 (m), 748 (m) cm^{-1}.

Example 3(x)

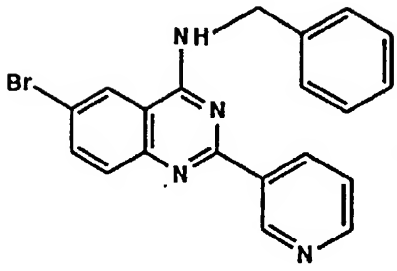
6-chloro-4-(2-(1 -methyl-2-pyrrolyl)ethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)
The product was collected by filtration as a white solid.
NMR (200MHz, DMSO-d6): δ 2.99 (t, 2H), 3.58 (s, 3H), 3.89 (q, 2H), 5.90 (m, 2H), 6.62 (m, 1H), 7.55 (m, 1H), 7.83 (m, 2H), 8.44 (d, 1H), 8.70-8.75 (m, 3H), 9.61 (m, 1H).
(2HCl salt)
The product was collected by filtration as a white powder.
mp : 190-194 °C (dec.).
NMR (200MHz, DMSO-d6): δ 3.02 (t, 2H), 3.58 (s, 3H), 3.97 (q, 2H), 5.88 (m, 2H), 6.60 (t, 1H), 7.97-8.14 (m, 2H), 8.16 (d, 1H), 8.74 (d, 1H), 8.99 (dd, 1H), 9.16 (d, 1H), 9.63 (d, 1H), 10.00 (broad, 1H).
IR (KBr): ν 711 (w), 709 (m), 1359 (m), 1388 (s), 1438 (m), 1549 (s), 1570 (s), 1599 (s), 1634 (s), 2065 (m), 2365 (m), 2555 (s), 3110 (m), 3360 (m) cm^{-1}.

Example 3(y)

4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline and its salt

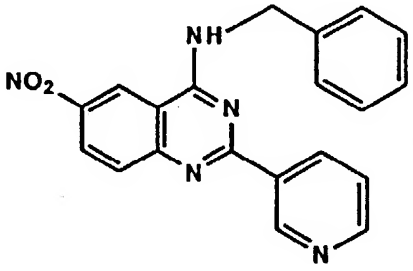


(2HCl)

(free base)
The product was collected by filtration as a solid.
NMR (200MHz, DMSO-d6): δ 4.90 (d, 2H), 7.25-7.56 (m, 6H), 7.75 (d, 2H), 7.94 (dd, 1H), 8.66-8.71 (m, 3H), 9.18 (broad, 1H), 9.54 (d, 1H).
(2HCl salt)
mp : 233-240 °C (dec.).
NMR (200MHz, DMSO-d6): δ 4.99 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.57 (m, 3H), 7.96-8.03 (m, 1H), 8.07-8.10 (m, 2H), 8.93-9.00 (m, 2H), 9.19 (d, 1H), 9.62 (d, 1H), 10.30 (broad, 1H).
IR (KBr): ν 701 (m), 1357 (m), 1404 (s), 1446 (m), 1519 (s), 1549 (s), 1628 (s), 2400-3000 (broad, s), 3140 (s) cm^{-1}.

Example 3(z)

4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline and its salt

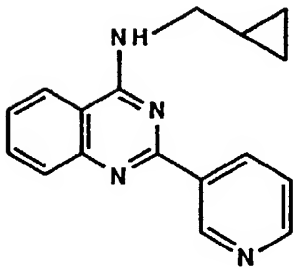


(2HCl)

(free base)
The product was collected by filtration as a solid.
NMR (200MHz, DMSO-d6): δ 4.95 (d, 2H), 7.25-7.40 (m, 3H), 7.48-7.58 (m, 3H), 7.93 (dd, 1H), 8.50 (dt, 1H), 8.70-8.80 (m, 2H), 9.46 (d, 1H), 9.58 (d, 1H), 9.70 (broad, 1H).
(2HCl salt)
mp : 289-292 °C (dec.).
NMR (200MHz, DMSO-d6): δ 5.00 (d, 2H), 7.25-7.42 (m, 3H), 7.51-7.55 (m, 2H), 8.04-8.09 (m, 2H), 8.59 (dt, 1H), 9.00 (dd, 1H), 9.27 (d, 1H), 9.54 (d, 1H), 9.67 (s, 1H), 10.18 (broad, 1H).
IR (KBr): ν 671 (m), 709 (m), 757 (m), 784 (m), 1349 (s), 1514 (s), 1578 (s), 1636 (s), 2445 (broad, s), 2860 (w), 3070 (m) cm^{-1}.

Example 3(aa)

4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

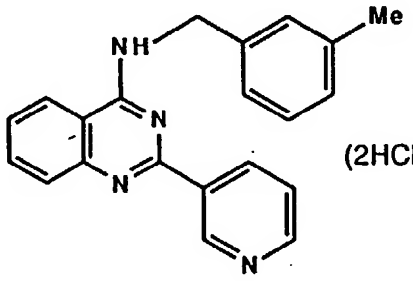


(2HCl)

(free base)
mp : 162-163 °C.
NMR (200MHz, DMSO-d6): δ 0.38 (m, 2H), 0.49 (m, 2H), 1.33 (m, 1H), 3.58 (t, 2H), 7.55 (m, 2H), 7.79 (m, 2H), 8.32 (d, 1H), 8.56 (t, 1H), 8.69 (m, 2H), 9.62 (s, 1H).
IR(KBr): ν 3265(w), 1537 (s), 1525 (s), 1437 (w), 1369 (s), 762 (m) cm^{-1}.
(2HCl salt)
mp : 230-239 °C
NMR (200MHz, DMSO-d6): δ 0.43 (m, 2H), 0.50 (m, 2H), 1.32 (m, 1H), 3.71 (t, 2H), 7.78 (t, 1H), 7.93 (m, 1H), 8.05 (t, 1H), 8.34 (d, 1H), 8.77 (d, 1H), 8.99 (d, 1H), 9.08 (dd, 1H), 9.68 (s, 1H), 10.68 (bs, 1H).
IR (KBr): ν 3405-2700 (broad, s), 2365 (w), 1632 (s), 1600 (s), 1570 (m), 1542 (m), 1458 (w), 1383 (m), 1321 (w), 767 (w), 669 (w) cm^{-1}.

Example 3(bb)

4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt

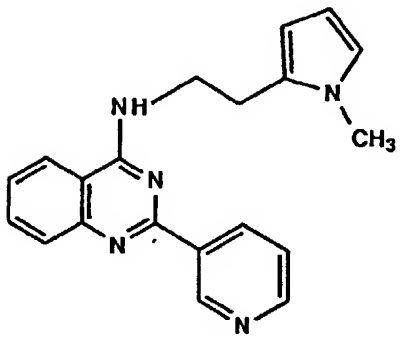


(2HCl)

(free base)
mp : 166-169 °C.
NMR (200MHz, DMSO-d6): δ 2.28 (s, 3H), 4.90 (s, 2H), 7.03 (bd, 1H), 7.18-7.32 (m, 3H), 7.47-7.61 (m, 2H), 7.81 (d, 1H), 8.35 (d, 1H), 8.69 (m, 2H), 9.02 (bt, 1H), 9.58 (s, 1H).
IR (KBr): ν 3245 (m), 1567 (s), 1533 (s), 1438 (m), 1443 (m),1368 (s), 1326 (m), 762 (m), 699 (m) cm^{-1}.
(2HCl salt)
mp : 225-244 °C.
NMR (200MHz, DMSO-d6): δ 2.29 (s, 3H), 5.03 (s, 2H), 7.10 (d, 1H), 7.20-7.38 (m, 3H), 7.77 (t, 1H), 7.92-8.10 (m, 2H), 8.34 (d, 1H), 8.76 (d, 1H), 9.02 (d, 2H), 9.20 (d, 2H), 9.69 (s, 1H), 11.05 (bt, 1H).
IR (KBr): ν 3400 (m), 3050-2600 (broad, m), 1627 (s), 1570 (s), 1542 (m), 1457 (m), 1385 (m), 770 (m), 680 (m) cm^{-1}.

Example 3(cc)

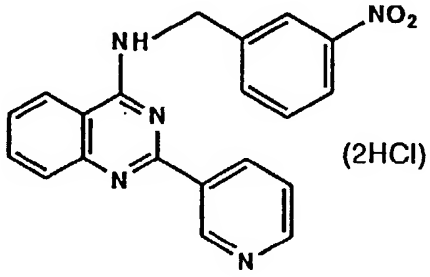
4-(2-(1-methyl-2-pyrrolyl)ethyl)amino-2-(3-pyridyl)quinazoline



mp : 140-142 °C.
NMR (200MHz, DMSO-d6): δ 3.00 (t, 2H), 3.58 (s, 3H), 3.88 (qd, 2H), 5.91 (m, 2H), 6.63 (t, 1H), 7.53 (m, 2H), 7.80 (d, 2H), 8.24 (d, 1H), 8.59 (t, 1H), 8.66-8.79 (m, 2H), 9.62 (s, 1H).
IR (KBr): ν 3445 (m), 3130-2900 (w), 2369 (w), 1567 (s), 1514 (s), 1533 (s), 1443 (m), 1438 (m), 1368 (s), 1351 (m), 1187 (w), 762 (m), 699 (m) cm^{-1}.

Example 3(dd)

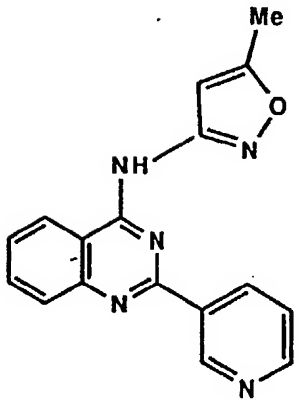
4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline and its salt



(free base)
mp : 218-220 °C.
NMR (200MHz, DMSO-d6): δ 5.05 (d, 2H), 7.46-7.69 (m, 3H), 7.83 (m, 2H), 7.84 (d,1H), 8.13 (d, 1H), 8.37 (m, 2H), 8.67 (m, 2H), 9.18 (t, 1H), 9.52 (s, 1H).
(2HCl salt)
mp : 263-265 °C.
NMR (200MHz, DMSO-d6): δ 5.15 (d, 2H), 7.60-7.86 (m, 3H), 7.90-8.19 (m, 5H), 8.26 (d, 1H), 8.43 (s, 1H), 8.75 (d, 1H), 9.00 (d, 1H), 9.18 (d, 1H), 9.65 (s, 1H), 11.03 (bs, 1H).

Example 3(ee)

4-(5-methyl-3-isoxazolyl)amino-2-(3-pyridyl)quinazoline and its salt



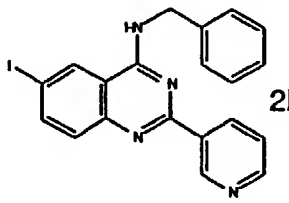
(2HCl)

(free base)
NMR (200MHz, DMSO-d6): δ 2.28 (s, 3H), 7.64 (s, 1H), 7.52-7.71 (m, 2H), 7.95 (m, 2H), 8.72 (m, 4H), 9.68 (m, 1H), 10.98 (s, 1H).
(2HCl salt)
mp : 228-230 °C.
NMR (200MHz, DMSO-d6): δ 2.53 (s, 3H), 7.09 (s, 1H), 7.74 (m, 1H), 8.04 (m, 2H), 8.18 (m, 1H), 8.75 (d, 1H), 9.06 (d, 1H), 9.34 (d, 1H), 9.64 (s, 1H).

The following compounds were obtained by the same procedure as described in Reference examples 2, 3, 4 and 5 and examples 1 and 2 or in Reference example 6, 7 and 8 and examples 1 and 2, by using isatoic anhydride.

Example 3(ff)

6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride

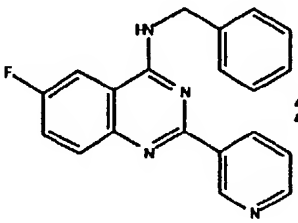


2HCl

mp : 205-10 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 5.00 (d, 2H), 7.28-7.41 (m, 3H), 7.47-7.53 (m, 2H), 7.80 (d, 1H), 7.95 (m, 1H), 8.23 (dd, 1H), 8.92-8.98 (m, 2H), 9.08 (d, 1H), 9.59 (m, 1H), 10.00 (broad, 1H).

Example 3(gg)

6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline dihydrochloride



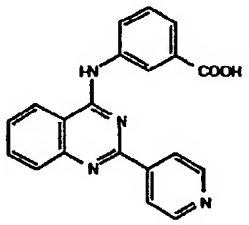
2HCl

mp : 200-2 °C, (dec.)

NMR (200MHz, DMSO-d6) δ: 5.02 (d, 2H), 7.28-7.41 (m, 3H), 7.51-7.54 (m, 2H), 7.82-8.02 (m, 2H), 8.07-8.20 (m, 1H), 8.40-8.52 (d, 1H), 8.97 (dd, 1H), 9.15 (d, 1H), 9.61 (s, 1H), 10.08 (broad, 1H).

Example 3(hh)

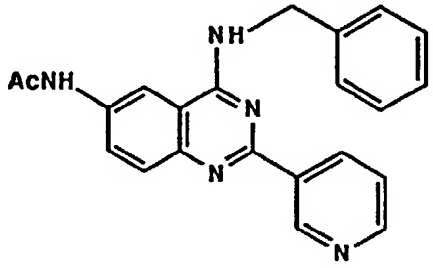
4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline



mp : >300°C
NMR (200MHz, DMSO-d6) δ: 7.65 (t, 1H), 7.78 (m, 2H), 7.99 (d, 2H), 8.22 (d, 1H), 8.68 (d, 2H), 8.75 (d, 1H), 8.87 (m, 3H), 10.44 (s, 1H).
IR (KBr) ν: 3370-2800 (w, broad), 1712 (m), 1632 (m),1571 (s), 1545 (s), 1473 (m), 1437 (m), 1376 (m), 764 (m) cm^{-1}.

Example 4

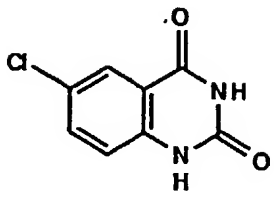
6-acetylamino-4-phenylmethylamino-2-(3-pyridyl)quinazoline



To warmed suspension of the nitroquinazoline compound (141 mg, prepared in Example 3(z)) in acetic acid (4 mL) was added zinc dust (80 mg). The red mixture was heated to reflux for overnight. After cooling down to room temperature the precipitate was removed by filtration. The filtrate was neutralized to pH 8 and extracted with chloroform. The insoluble solid was removed by filtration during the extraction. The chloroform was dried over potassium carbonate and then concentrated to 0.5 mL (total volume). The precipitate was collected by filtration to give the title compound (20 mg) having the following physical data.
mp : 127 °C (dec.).
NMR (200MHz, DMSO-d6): δ 2.12 (s, 3H), 4.88 (d, 2H), 7.22-7.37 (m, 3H), 7.45-7.53 (m, 2H), 7.75 (m, 1H), 8.32 (m, 2H), 8.58-8.69 (m, 3H), 8.94 (broad, 1H), 9.52 (m, 1H), 10.23 (broad, 1H).
IR (KBr): ν 700 (w), 840 (w), 1318 (m), 1368 (m), 1426 (m), 1537 (s), 1584 (s), 1676 (m), 3065 (m), 3365 (m) cm^{-1}.

Reference example 11

6-chloro-(1H,3H)-quinazolin-2,4-dione

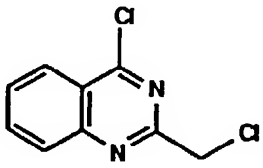


To a solution of 5-chloroanthranilamide (3.4 g) in tetrahydrofuran (50 mL) was added phosgene (16 mL, 1.93M solution in toluene) via an addition funnel. The reaction mixture was stirred at room temperature for 4 hours and then heated to reflux for another two hours. The reaction mixture was concentrated to a total volume about 10 mL. After cooling, the title compound (3.72 g) having the following physical data, was collected by filtration and dried in vacuum.

NMR (200MHz, DMSO-d6): δ 7.19 (d, 1H), 7.69 (dd, 1H), 7.82 (d, 1H), 11.28 (broad, 1H), 11.45 (broad, 1H).

Reference example 12

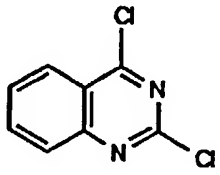
4-chloro-2-chloromethylquinazoline



To a solution of anthranilonitrile (11.8 g) and chloroacetonitrile (7.5 g) in 1,4-dioxane (200 mL), cooled in an ice bath, was bubbled HCl gas. The reaction mixture was stirred for two and one-half hours at which time the reaction was allowed to warm to room temperature and continued to bubble HCl gas for 16 hours. After the HCl gas bubbling was ceased, nitrogen gas was bubbled through to remove any unreacted HCl gas. The mixture was concentrated at 45 °C in vacuo. The mixture was partitioned between methylene chloride (300 mL) and water (400 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was dissolved in 200 mL of warm hexane, filtered and allowed to cool to room temperature. The title compound (9.1 g) was collected by filtration.

Reference example 13

2,4-dichloroquinazoline

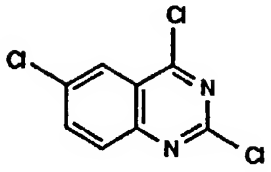


A mixture of benzoyleneurea (20.0 g), phosphorus oxychloride (100 mL) and N,N-dimethylaniline (12 mL) was refluxed for five hours. After stirring overnight at room temperature, the mixture was heated to reflux once more for an additional four hours. The cooled mixture was then poured into ice and the precipitate collected. The precipitate was purified on silica gel column with 5% methanol/chloroform as eluent. The isolated product was triturated in ether/hexane and collected to obtain the title compound (6.9 g).

The following compound was obtained by the same procedure as Reference example 13, by using 6-chloro-(1H,3H)-quinazolin-2,4-dione prepared by Reference example 11.

Reference example 13(a)

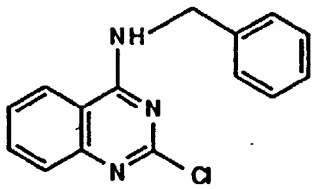
2,4,6-trichloroquinazoline



mp : 125 °C.
NMR (200MHz, DMSO-d6): δ 8.09 (d, 1H), 8.21 (dd, 1H), 8.33 (d, 1H).

Reference example 14

4-phenylmethylamino-2-chloroquinazoline

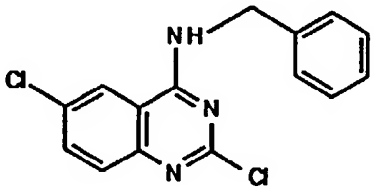


The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the dichloroquinazoline prepared in Reference example 13 and phenylmethylamine (equivalent to dichloroquinazoline).
mp : 178-180 °C.
NMR ($CDCl_3$): δ 86 (d, 2H), 6.05 (s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).

The following compounds were obtained by the same procedure as Reference example 14, by using the corresponding 4-chloro compounds prepared in Reference example 13(a) and 12, respectively.

Reference example 14(a)

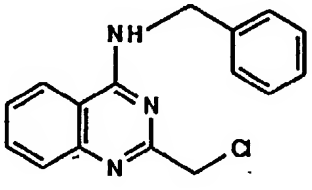
4-phenylmethylamino-2,6-dichloroquinazoline



NMR (200MHz, DMSO-d6): δ 4.74 (d, 2H), 7.28-7.43 (m, 5H), 7.67 (d, 1H), 7.85 (dd, 1H), 8.50 (d, 1H), 9.36 (broad, 1H).

Reference example 14(b)

4-phenyl methylamino-2-chloromethylquinazoline

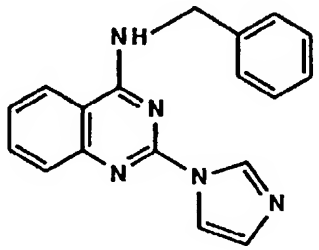


mp : 137-139 °C.

NMR ($CDCl_3$):δ 4.68 (s, 2H), 4.90 (d, 2H), 6.00 (bs, 1H), 7.27-7.90 (m, 9H).

Example 5

4-phenylmethylamino-2-(1-imidazolyl)quinazoline



A mixture of the 2-chloro compound (0.81 g, prepared in Reference example 14), imidazole (0.81 g) and phenol (3.0 g) was heated to reflux for four and one-half hours. The mixture was then taken up in chloroform, washed twice with sodium hydroxide solution, dried over anhydrous potassium carbonate and concentrated. The concentrate was triturated in ether and collected to obtain the title compound (0.7 g) as a yellow solid having the following physical data.

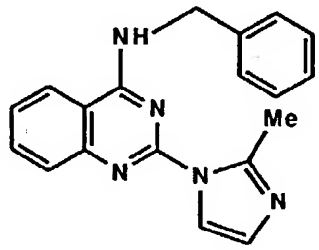
mp : 212-214°C.

NMR ($CDCl_3$):δ 4.86 (d, 2H), 6.05 (broad s, 1H), 7.32-7.51 (m, 6H), 7.62-7.85 (m, 3H).

The following compounds were obtained by the same procedure as Example 5, by using 4-phenylmethylamino-2-chloroquinazoline prepared in Reference example 14, 14(a) and 14(b) or corresponding qunazoline, and the proper heterocyclic compounds.

Example 5(a)

4-phenylmethylamino-2-(2-methyl-1-imidazolyl)quinazoline



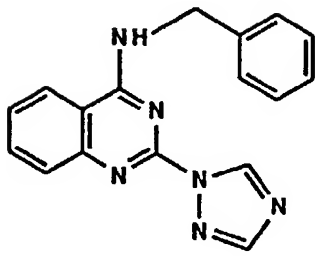
mp : 182-186 °C.

NMR ($CDCl_3$): δ 2.89 (s, 3H), 4.92 (d, 2H), 6.30 (broad, 1H), 6.97 (s, 1H), 7.30-7.50 (m, 5H), 7.73-7.82 (m, 3H), 7.96 (s, 1H).

IR (KBr): ν 3240 (w), 3060 (w), 1618 (m), 1595 (s), 1559 (s), 1439 (m), 1403 (s), 1380 (s), 1305 (s), 766 (w), 696 (w) cm^{-1}.

Example 5(b)

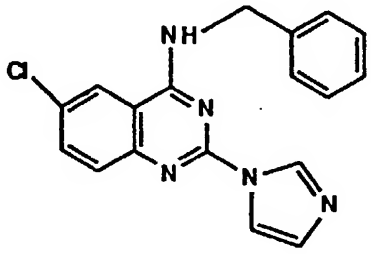
4-phenylmethylamino-2-(1,2,4-triazol-1-yl)quinazoline



mp : 193-195 °C.
NMR ($CDCl_3$): δ 4.73 (d, 2H), 6.02 (bs, 1H), 7.1-7-7.74 (m, 8H), 7.59-7.65 (m, 3H).
IR (KBr): ν 3240 (w), 3125 (w), 1618 (m), 1596 (s), 1580 (s), 1547 (s), 1491 (m), 1384 (s), 1314 (s), 1207 (s), 1052 (w), 763 (m), 698 (m) cm^{-1}.

Example 5(c)

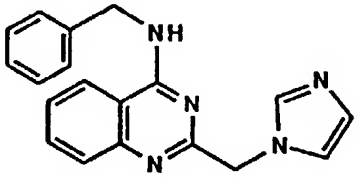
4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline



mp : 260-264 °C (dec.).
NMR (200MHz, DMSO-d6): δ 4.84 (d, 2H), 7.09 (s, 1H), 7.28-7.50 (m, 5H), 7.70 (d, 1H), 7.82 (dd, 1H), 7.93 (s, 1H), 8.52 (d, 1H), 8.56 (s, 1H), 9.40 (broad. 1H).

Example 5(d)

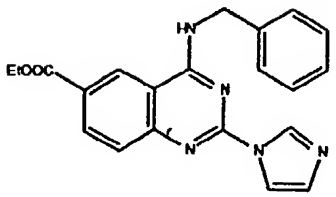
4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline



mp : 174 - 176 °C.
NMR (200MHz, DMSO-d6): δ 4.70 (d, 2H), 5.18 (s, 2H), 6.88 (s, 1H), 7.16 (s, 1H), 7.17-7.40 (m, 4H), 7.50 (m, 1H), 7.60-7.82 (m, 3H), 8.28 (d, 1H), 8.92 (m, 1H).

Example 5(e)

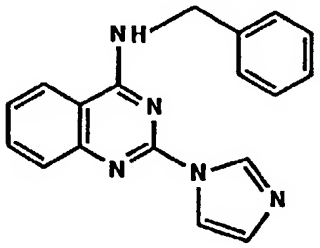
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline



mp : 193 °C (dec.)
NMR (200MHz, CDCl3) δ: 1.58 (t, 3H), 4.69-4.80(m, 4H), 6.62 (br, 1H), 7.17 (s, 1H), 7.35-7.44 (m, 5H), 7.89 (d, 1H), 7.98 (s, 1H), 8.24 (dd, 1H), 8.58 (d, 1H), 8.67 (s, 1H).
IR (KBr) ν: 3275, 1652, 1626, 1588, 1472, 1438, 1314, 1093, 1055, 1014 cm^{-1}.

Example 6

4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

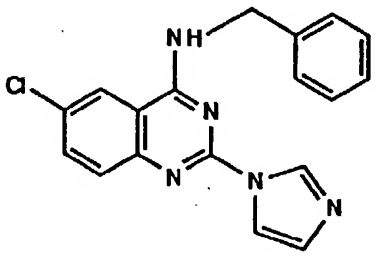


2HCl

The title compound having the following physical data, was obtained by the same procedure as Example 2, by using the free base prepared in Example 5 and HCl/methanol solution.
mp : 248-250 °C.
NMR (200MHz, DMSO-d6): δ 4.96 (d, 2H), 7.20-7.40 (m, 3H), 7.50-7.54 (m, 2H), 7.63 (t, 1H), 7.75-7.81 (m, 1H), 7.88-7.90 (m, 2H), 8.43 (s, 1H), 8.55 (d, 1H), 9.85 (broad t, 1H), 10.03 (s, 1H).
IR (KBr): ν 3055 (broad), 2655 (broad), 1634 (s), 1569 (s), 1520 (m), 1472 (m), 1395 (s), 760 (w) cm^{-1}.
By the same procedure as described in Reference example 13 and 14 and Example 5 and 6, the below compounds having the following physical data were given.

Example 6(a)

4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline dihydrochloride

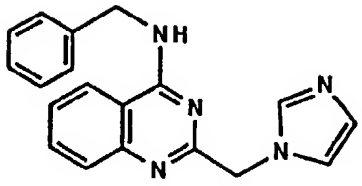


2HCl

mp : 186 °C (dec.).
NMR (200MHz, DMSO-d6): δ 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.78 (d, 1H), 7.90 (t, 1H), 7.92 (dd, 1H), 8.43 (t, 1H), 8.71 (d, 1H), 9.88 (broad, 1H), 10.03 (t, 1H).

Example 6(b)

4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline dihydrochloride

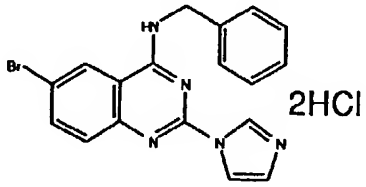


mp : 306 °C(dec.).
NMR (200MHz, DMSO-d6): δ 4.64 (m, 2H), 5.81 (s, 2H), 7.17-7.40 (m, 5H), 7.68-8.10 (m, 5H), 8.68 (m, 1H), 9.26 (s, 1H).

The following compound was obtained by the same procedure as described in Reference example 13, 14 and example 5 and 6, by using the corresponding (1H,3H)-quinazoline-2,4-dione or its derivative and corresponding amine.

Example 6(c)

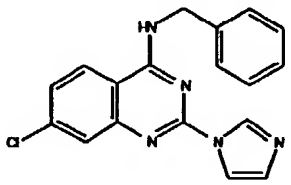
6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 199-202 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.70 (d, 1H), 7.81 (t, 1H), 8.01 (dt, 1H), 8.38 (d, 1H), 8.81 (d, 1H), 9.80 (broad, 1H), 9.88 (d, 1H).

Example 6(d)

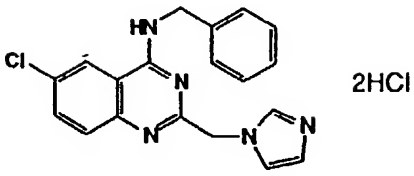
7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline



mp : 265-268° C
NMR (200MHz, DMSO-d6) :δ 4.85 (s, 2H), 7.08 (s, 1H), 7.21-7.40 (m, 3H), 7.42-7.58 (m, 2H), 7.71 (s, 1H), 7.91 (s, 1H), 8.35 (d, 1H), 8.54 (s, 1H).
IR (KBr): ν 3260 (w), 3135 (w), 1609 (s), 1570 (s), 1473 (s), 1451 (s), 1418 (s), 1349 (m), 1307 (m), 1037 (m), 778 (w), 698 (w) cm^{-1}.

Example 6(e)

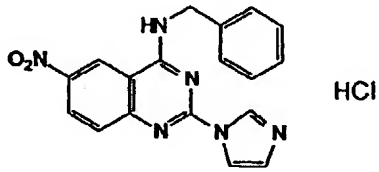
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline dihydrochloride



mp : 290 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 4.66 (d, 2H), 5.72 (s, 2H), 7.18-7.42 (m, 5H), 7.72-8.05 (m, 4H), 8.76 (s, 1H), 9.27 (s, 1H).

Example 6(f)

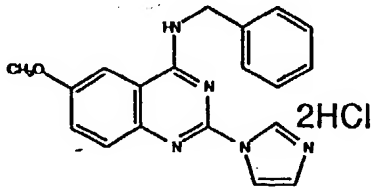
6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride



mp : 190 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 5.00 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.53 (m, 2H), 7.76 (broad, 1H), 7.87-7.93 (d, 1H), 8.39 (broad, 1H), 8.57-8.65 (d, 1H), 9.56 (s, 1H), 9.82 (broad, 1H), 10.28 (broad, 1H).
IR (KBr) ν: 1335(s), 1403(s), 1438(w), 1518(w), 1601(s), 3405(broad), 3445(w) cm^{-1}.

Example 6(g)

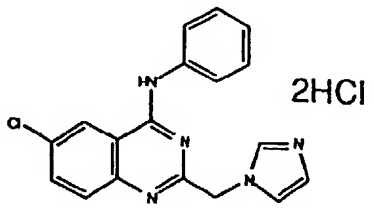
6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 196 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 3.93 (s,3H), 4.98 (m, 2H), 7.25-7.42 (m, 3H), 7.45-7.57 (m, 2H), 7.74 (d, 1H), 7.87 (d, 1H), 7.95 (d, 1H), 8.41 (d, 1H), 9.55 (broad, 1H), 9.96 (d, 1H).
IR (KBr) ν: 1254(m), 1395(s), 1506(m), 1558(s), 1601(s), 3065(w), 3245(w), and 3395(w) cm^{-1}.

Example 6(h)

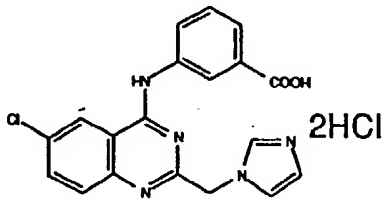
6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline dihydrochloride



mp : 280 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 5.72 (s, 2H), 7.12-8.03 (m, 9H), 8.99 (m, 1H), 9.26 (s, 1H), 10.65 (bs, 1H).
IR (KBr) ν: 3100 (m), 2830 (m), 2565 (m), 1635 (m), 1608 (m), 1578 (sd), 1492 (ms), 1151 (m) cm^{-1}.

Example 6(i)

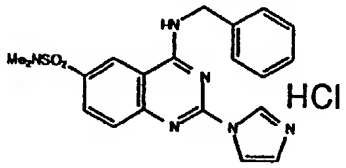
6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline dihydrochloride



mp : 285 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 5.69 (s, 2H), 7.49 (t, 1H), 7.70-8.02 (m, 6H), 8.26 (m, 1H), 8.90 (m, 1H), 9.26 (s, 1H), 10.50 (bs, 1H).
IR (KBr) ν: 3326 (m), 3065 (m), 2835 (m), 1698 (m), 1631 (m), 1602 (m), 1561 (s), 1486 (m), 1444 (m), 1400 (m), 1376 (mw) cm^{-1}.

Example 6(j)

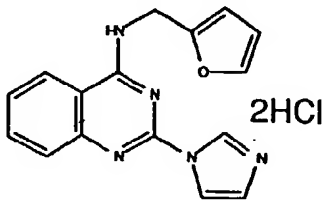
6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride



mp : 264-266°C.
NMR (200MHz, DMSO-d6) δ: 2.69(s, 6H), 5.00(d, 2H), 7.25-7.45(m, 3H), 7.46-7.54(m, 2H), 7.78(m, 1H), 7.93(dd, 1H), 8.13(d, 1H), 8.40(m, 1H), 8.95(m, 1H), 9.84(m, 1H), 10.13(br, 1H).
IR (KBr): ν 3400(m), 3320(m), 2960(w), 1597(s), 1556(m), 1520(m), 1445(m), 1398(s), 1341(s), 1164(s), 728(s), 579(s) cm^{-1}.

Example 6(k)

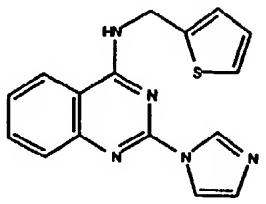
4-(2-furylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 230 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 4.99 (d, 2H), 6.48 (m, 2H), 7.57-7.97 (m, 5H), 8.49 (m, 2H), 9.64 (t, 1 H), 10.08 (s, 1 H).

Example 6(l)

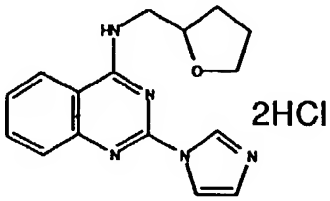
4-(2-thienylmethyl)amino-2-(1-imidazolyl)quinazoline



mp : 234-235° C
NMR (200MHz, DMSO-d6): δ 5.03 (d, 2H), 7.00 (m, 1H), 7.13 (s, 1H), 7.18 (d, 1H), 7.37 (d, 1H), 7.52 (t, 1H), 7.78 (m, 2H), 8.02 (s, 1H), 8.28 (d, 1H), 8.67 (s, 1H), 9.40 (t, 1H).
IR (KBr): ν 3255 (w, broad), 1617 (w), 1668 (s), 1470 (s), 1402 (s), 1321 (m) cm^{-1}.

Example 6(m)

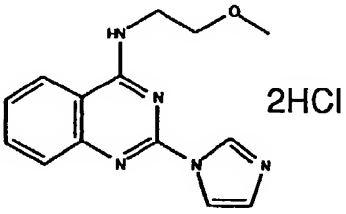
4-(2-tetrahydrofuranylmethyl)amino-2-(1-imidazolyl)quinazoline



mp : 98-150 °C
NMR (200MHz, DMSO-d6) δ: 1.62-2.13 (m, 4H), 3.62-3.90 (m, 4H), 4,12-4.31 (m, 2H), 7.54-7.97 (m, 4H), 8.44 (s, 1H), 9.32 (t, 1H), 10.02 (s, 1H).
IR (KBr) ν: 3500-2700 (s, broad), 1635 (m), 1576 (m), 1396 (m), 1063 (w), 765 (w) cm^{-1}.

Example 6(n)

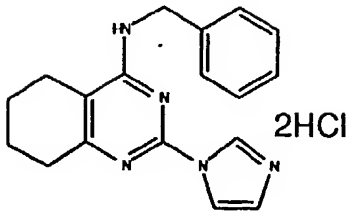
4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 210-215 °C
NMR (200MHz, DMSO-d6) δ: 3.31 (s, 3H), 3.66 (t, 2H), 3.85 (q, 2H), 7.61 (t, 1 H), 7.78 (d, 1H), 7.85 (m, 1H), 8.42 (m, 2H), 9.23 (t, 1H), 9.95 (s, 1H).

Example 6(o)

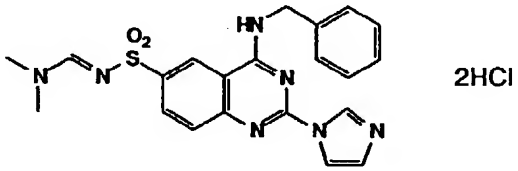
4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydro-quinazoline dihydrochloride



mp : 195 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 1.79 (m, 4H), 2.45 (m, 2H), 2.66 (m, 2H), 4.74 (d, 2H), 7.17-7.48 (m, 5H), 7.83 (cs, 1H), 8.13 (t, 1H), 8.24 (cs, 1H), 9.84 (cs, 1H).

Example 6(p)

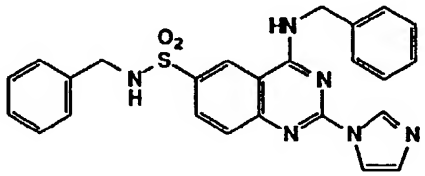
6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 225 °C
NMR (200MHz, DMSO-d6) δ: 2.93 (s, 3H), 3.18 (s, 3H), 4.97 (d, 2H), 7.25-7.40 (m, 3H), 7.49-7.53 (m, 2H), 7.79 (s, 1H), 7.84 (d, 1H), 8.15 (dt, 1H), 8.30 (s, 1H), 8.39 (s, 1H), 9.00 (s, 1H), 9.86 (s, 1H), 10.10 (t, 1H).

Example 6(q)

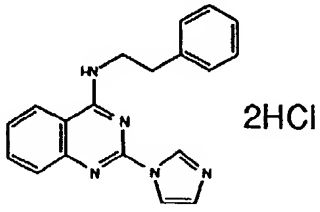
6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline



mp : 207-8 °C
NMR (200MHz, DMSO-d6) δ: 4.09 (d, 2H), 4.89 (m, 2H), 7.11 (s, 1H), 7.16-7.52 (m, 10H), 7.79 (d, 1H), 7.96 (d, 1H), 8.07 (dd, 1H), 8.28 (t, 1H), 8.60 (s, 1H), 8.83 (m, 1H), 9.80 (broad t, 1H).

Example 6(r)

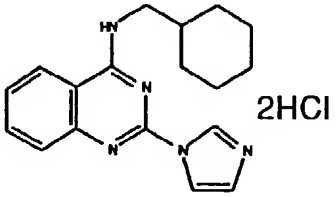
4-(2-phenylethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 70-100 °C
NMR (200MHz, DMSO-d6) δ: 3.05 (t, 2H), 3.95 (q, 2H), 7.12-7.38 (m, 6H), 7.57 (t, 1H), 7.73 (m, 2H), 7.89 (m, 3H), 8.41 (m, 2H), 9.38 (t, 1 H), 9.96 (s, 1H).

Example 6(s)

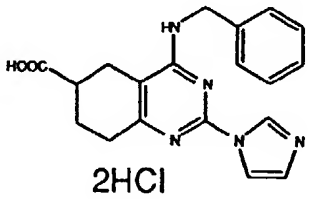
4-cyclohexylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 140-150 °C
NMR (200MHz, DMSO-d6) δ: 0.98-1.32 (m, 5H), 1.53-1.90 (m, 6H), 3.58 (t, 2H), 7.59 (t, 1H), 7.77 (m, 1H), 7.89 (t, 2H), 8.41 (s, 1H), 8.56 (d, 1H), 9.28 (t, 1 H), 9.97 (s, 1 H).

Example 6(t)

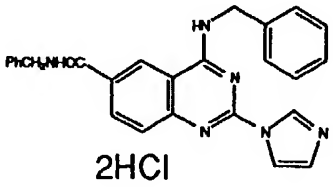
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride



mp : 105 °C (dec.)
NMR (200MHz, DMSO-d6) δ: 1.82 (m, 1H), 2.10 (m, 1H), 2.71 (m, 5H), 4.74 (d, 2H), 7.18-7.47 (m, 5H), 7.82 (s, 1H), 8.24 (s, 1H), 8.25 (m, 1H), 9.84 (s, 1H).
IR (KBr) ν: 3140 (bm), 2935 (bm), 1718 (mw), 1654 (m), 1617 (ms), 1522 (mw), 1394 (m) cm^{-1}.

Example 6(u)

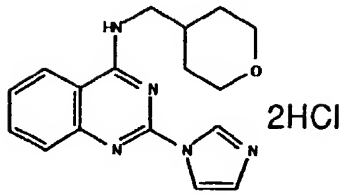
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 235-237 °C
NMR (200MHz, DMSO-d6) δ: 4.54 (d, 2H), 7.20-7.40 (m, 8H), 7.48-7.52 (m, 2H), 7.70 (s, 1H), 7.81 (d, 1H), 8.31 (dd, 1H), 8.37 (s, 1H), 9.09 (s, 1H), 9.22 (br, 1 H), 9.82 (s, 1 H), 9.89 (br, 1H).
IR (KBr) ν: 3500-3000 (br), 1647, 1604 ,1555, 1453, 1398, 1315, 699cm^{-1}.

Example 6(v)

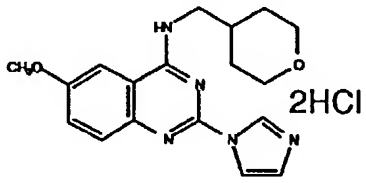
4-(4-tetrahdyropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 160-195 °C
NMR (200MHz, DMSO-d6) δ: 10.0 (m, 1H), 9.29 (m, 1H), 8.53 (d, 1H), 8.45 (m, 1H), 7.82-7.95 (d, 2H), 7.75 (d, 1H), 7.60 (t, 1H), 3.86 (m, 2H), 3.64 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.21-1.48 (m, 2H).
IR (KBr) ν: 1635, 1604, 1562, 1524, 1471, 1443, 1393, 1091, 762 cm^{-1}.

Example 6(w)

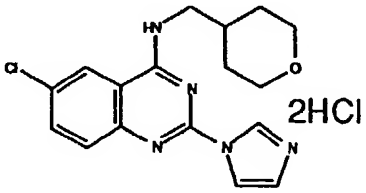
6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 170-190 °C
NMR (200MHz, DMSO-d6) δ: 9.96 (s, 1H), 9.15 (m, 1H), 9.42 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H) 7.71 (d, 1H), 7.52 (dd, 1H), 3.94 (s, 3H), 3.80-3.95 (m, 2H), 3.62 (m, 2H), 3.29 (t, 2H), 2.02 (m, 1H), 1.60-1.75 (m, 2H), 1.20-1.49 (m, 2H).
IR (KBr) ν: 1637, 1605, 1569, 1524, 1473, 1440, 1391, 1251, 1091, 1020 cm^{-1}.

Example 6(x)

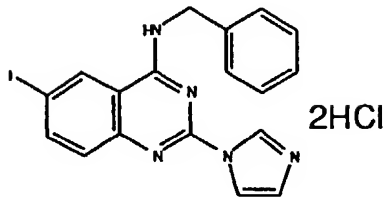
6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 155-185 °C
NMR (200MHz, DMSO-d6) δ: 9.89 (s, 1H), 9.25 (m, 1H), 8.66 (m, 1H), 8.41 (m, 1H), 7.72-7.96 (m, 3H), 3.81-3.95 (m, 2H), 3.56-3.70 (m, 2H), 3.28 (t, 2H), 2.02 (m, 1H), 1.63-1.79 (m, 2H), 1.20-1.46 (m, 2H).
IR (KBr) ν: 1604, 1577, 1524, 1497, 1446, 1396, 1349, 1089 cm^{-1}.

Example 6(y)

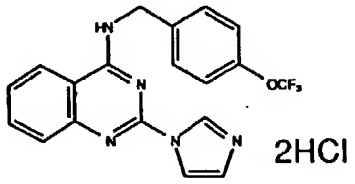
6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 183 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 4.95 (m, 2H), 7.25-7.40 (m, 3H), 7.45-7.60 (m, 3H), 7.88 (t, 1H), 8.16 (dt, 1H), 8.43 (t, 1H), 8.93 (s,1H), 9.78 (t, 1H), 10.01 (d, 1H).
IR (KBr) ν: 3060, 2685, 1634, 1600, 1541, 1406, 1390 cm^{-1}.

example 6(z)

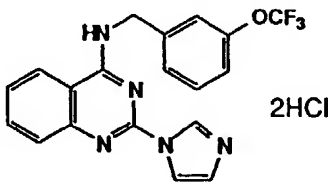
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1 -imidazolyl)quinazoline dihydrochloride



mp : 140-145 °C
NMR (200MHz, DMSO-d6) δ: 5.01 (m, 2H), 7.30-7.40 (m, 2H), 7.60-7.88 (m, 6H), 8.42-8.55 (m, 2H), 9.78 (bm, 1H), 10.35 (s, 1H).
IR (KBr) ν: 3070, 1634, 1604, 1560, 1525, 1394, 1263, 1224, 1164cm^{-1}.

Example 6(aa)

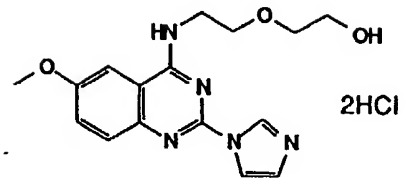
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1 -imidazolyl)quinazoline dihydrochloride



(2HCl salt)
mp : 170-180°C
NMR (200MHz, DMSO-d6): δ 5.01 (d, 2H), 7.25(d, 1H), 7.42-7.71 (m, 3H), 7.81(s, 1H), 7.88(m, 2H), 8.44(s, 1H), 8.54(d, 1H), 9.95(t, 1H), 10.06(s, 1H).
IR(KBr): ν 3430(w), 3020(w), 2960(w), 1653(s), 1603(s), 1542(m), 1396(s), 1270(s), 1216(m) cm^{-1}

Example 6(bb)

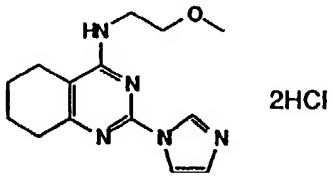
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)
mp : 167.5-170°C
NMR (200MHz, DMSO-d6): δ 3.51 (s, 4H), 3.75-3.78(m, 2H), 3.85-3.90(m, 2H), 3.93(s, 3H), 7.49(dd, 1H), 7.70(d, 1H), 7.84(t, 1H), 7.98(m, 1H), 8.39(m, 1H), 9.19(br, 1H), 9.90(t, 1H).
IR(KBr): ν 3270(s), 2940(m), 1610(s), 1557(m), 1513(s), 1396(s), 1247(m), 1115(m), 1029(w) cm -1

Example 6(cc)

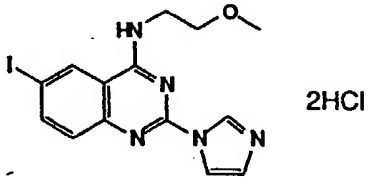
4-(2-methoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride



(2HCl salt)
mp : 140-142.5°C
NMR (200MHz, DMSO-d6): δ 1.77(s, 4H), 2.38(s, 2H), 2.65(s, 2H), 3.28(s, 3H), 3.54(t, 3H), 3.57(d, 2H), 7.49(br, 1H), 7.84(s, 1H), 8.30(s, 1H), 9.86(s, 1H).
IR(KBr): ν 3230-2355(br, m), 1555(s), 1506(s), 1526(s), 1449(w), 1395(s), 1101(m), 828(w), 756(m) cm $^{-1}$

Example 6(dd)

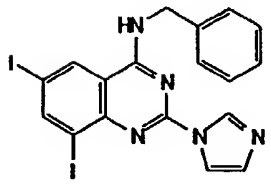
4-(2-methoxyethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)
mp : 159-161°C
NMR (200MHz, DMSO-d6): δ 3.31 (s, 3H), 3.67(t, 2H), 3.88(t, 2H), 7.54(d, 1H), 7.85(t, 1H), 8.13(dd, 1H), 8.42(t, 1H), 8.89(d, 1H), 9.20(t, 1H), 9.94(t, 1H).
IR(KBr): ν 3205-2365(m, br), 1633(s), 1604(s 1564(s), 1541(s), 1506(s), 1459(m), 1409(s), 1367(s), 1193(w), 1114(m), 1011(m), 859(w), 833(m), 777(m), 713(w), 621(w), 526(w) cm -1

Example 6(ee)

4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline dihydrochloride

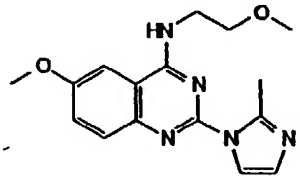


2HCl

(2HCl salt)
mp : 303-304°C (dec.)
NMR (200MHz, DMSO-d6): δ 4.94(d, 2H), 7.33(dd, 3H), 7.49(dd, 2H), 7.74(t, 1 H), 8.24(t, 1 H), 8.67(t, 1H), 8.88(d, 1H), 9.66(s, 1H), 9.77(br, 1H).
IR(KBr): ν 3410-2365(br, m), 1599(s), 1437(m), 1387(s), 1350(m), 1314(m), 1273(w), 1061(w), 1020(w), 793(w), 748(w), 701(w), 620(w) cm -1

Example 6(ff)

4-(2-methoxyethyl)amino-6-methoxy-2-(2-methyl-1-imidazolyl)quinazoline dihydrochloride

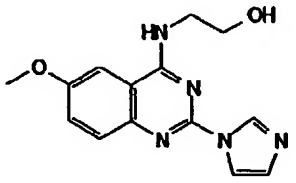


2HCl

(2HCl salt)
mp : 263-264°C
NMR (200MHz, DMSO-d6): δ 3.04(s 3H), 3.31 (s 3H), 3.68(m, 2H), 3.84(m, 2H), 3.92(s, 3H), 7.50(dd, 2H), 7.72(m, 2H), 7.91(s, 1H), 8.30(s, 1H), 9.10(m, 1H).
IR(KBr): ν 3230(w), 2680(w), 1615(s), 1592(s), 1560(s), 1420(m), 1382(m), 1248(m), 909(w) cm^{-1}

Example 6(gg)

4-(2-hydroxyethyl)amino-6-methoxy-2-(1 -imidazolyl)quinazoline dihydrochloride

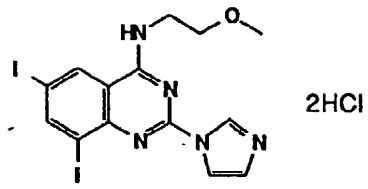


2HCl

(2HCl salt)
mp : 228-233°C
NMR (200MHz, D_2O):δ 3.63(t, 2H), 3.74(s, 3H), 3.83(t, 2H), 6.90(d, 1H), 7.16(dd, 1H), 7.26(d, 1H), 7.57(d, 1H), 7.96(d, 1H), 9.23(s, 1H).
IR(KBr): ν 2700-3400(br), 1605(s), 1569(m), 1520(m), 1394(m), 1246(w), 1040(w), 815(w) cm -1

Example 6(hh)

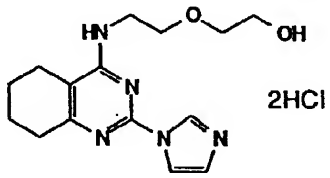
4-(2-methoxyethyl)amino-6,8-diiodo-2-(1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)
mp : 244-246.5°C
NMR (200MHz, DMSO-d6): δ 3.31(3H), 3.65(2H), 3.89(2H), 7.79(s, 1H), 8.29(s, 1H), 8.68(s, 1H), 8.89(s, 1H), 9.32(br, 1H).
IR(KBr): ν 3240-2335(br, m), 1598(s), 1553(w), 1523(w), 1476(m), 1436(m), 1383(m), 1354(m), 1275(w), 1107(w), 1086(m), 1018(m), 991(w), 860(w), 793(m), 752(w), 724(w), 615(w) cm -1

Example 6(ii)

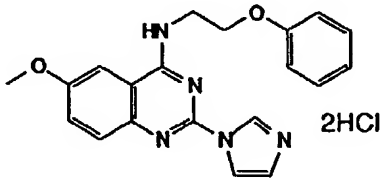
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride



(2HCl salt)
mp : 125-128°C
NMR (200MHz, DMSO-d6): δ 1.80(4H), 2.40(2H), 3.65(br, 8H), 7.45(br, 1H), 7.85(d, 1H), 8.30(d, 1H), 9.85(d, 1H).
IR(KBr): ν 3380(s), 3120(s), 2945(m), 2755-2460(m), 1615(s), 1540(s), 1457(m), 1428(m), 1390(s), 1350(m), 1319(w), 1103(m), 1070(m), 829(w), 624(w) cm $^{-1}$

Example 6(jj)

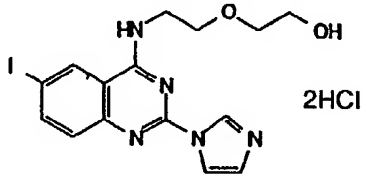
4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline and its dihydrochloride



(free base)
mp : 213-214°C
NMR (200MHz, DMSO-d6): δ 3.89 (s, 3H), 4.04(d, 2H), 4.31 (t, 2H), 6.93-7.01(3H), 7.08(d, 1H), 7.28(td, 2H), 7.45(dd, 1H), 7.64(d, 1H), 7.78(d, 1H), 7.93(t, 1H), 8.57(s, 1H), 9.85(br, 1H).
IR(KBr): ν 1599(s), 1555(s), 1491(s), 1409(s), 1382(w), 1310(m), 1242(s), 1051(s), 752(w) cm^{-1}
(2HCl salt)
mp : 184-186°C
NMR (200MHz, DMSO-d6): δ 3.94(s, 3H), 4.12(d, 2H), 4.33(t, 2H), 6.90-7.01(3H), 7.29(t, 2H), 7.53(dd, 1H), 7.88(t, 1H), 7.96(d, 1H), 8.40(t, 1H), 9.31(br, 1H), 9.93(d, 1H).
IR(KBr): ν 3050(m), 2840-2335(m), 1637(s), 1598(s), 1497(m), 1472(m), 1380(s), 1258(s), 1122(w), 1077(w), 1029(m), 775(m), 747(m) cm $^{-1}$

Example 6(kk)

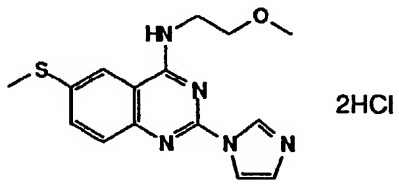
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline and its dihydrochloride



(free base)
NMR (200MHz, DMSO-d6): δ 3.50(s, 4H), 3.75(dd, 2H), 3.78(d, 2H), 4.59(br, 1H), 7.10(d, 1H), 7.47(dd, 1H), 7.95(d, 1H), 8.05(d, 1H), 8.52(d, 1H), 8.75(s, 1H), 8.57(br, 1H).
(2HCl salt)
mp : 132-135°C
NMR (200MHz, DMSO-d6): δ 3.50(s, 4H), 3.75(d, 2H), 3.86(d, 2H), 7.53(d, 1H), 7.83(s, 1H), 8.15(dd, 1H), 8.40(s, 1H), 8.89(d, 1H), 9.22(br, 1H), 9.90(s, 1H).
IR(KBr): ν 3230-2720(br, m), 1607(s), 1555(m), 1526(m), 1492(m), 1445(m), 1394(s), 1348(m), 1118(m), 1063(m), 1027(m), 859(m), 622 cm^{-1}

Example 6(ll)

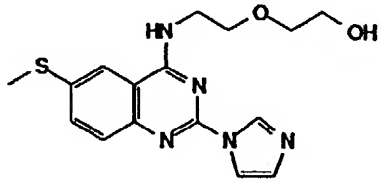
4-(2-methoxyethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline and its dihydrochloride



(free base)
mp : 201-202°C
NMR (200MHz, DMSO-d6): δ 2.61 (s, 3H), 3.32(s, 3H), 3.65(m, 2H), 3.81(m, 2H), 7.10(s, 1H), 7.58-7.73(m, 2H), 7.95(s, 1H), 8.10(s, 1H), 8.59(s, 1H), 8.83(t, 1H).
(2HCl salt)
mp : 230-232°C
NMR (200MHz, DMSO-d6): δ 2.65(s, 3H), 3.31(s, 3H), 3.66(m, 2H), 3.88(m, 2H), 7.64-7.83(m, 2H), 7.89(s, 1H), 8.24(m, 1H), 8.42(s, 1H), 9.28(t, 1H), 9.98(s, 1H).

Example 6(mm)

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline

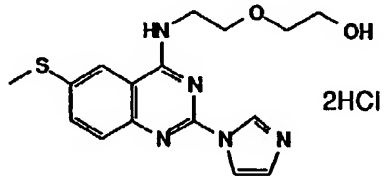


(free base)
mp : 169-172 °C
NMR (200MHz, DMSO-d6): δ 2.61 (s 3H), 3.51 (s 4H), 3. 76(m, 4H), 4.60(m, 1H), 7.10(s, 1H), 7.57-7.76(m,

2H), 7.95(s, 1H), 8.09(s, 1H), 8.59(s, 1H), 8.82(m, 1H).

Example 6(nn)

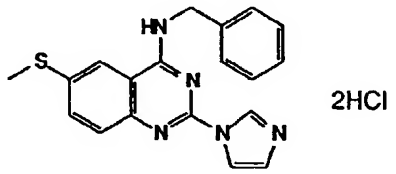
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline dihydrochloride



(2HCl salt)
mp : 180-182 °C.
NMR (200MHz, DMSO-d6): δ 2.65(s 3H), 3.51 (s, 4H), 3.75(m, 2H), 3.90(m, 2H), 7.64-7.82(m, 2H), 7.87(m, 1H), 8.26(m, 1H), 8.42(1H), 9.34(t, 1H), 9.98(m, 1H).

Example 6(oo)

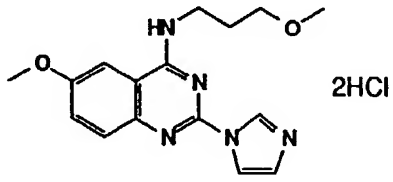
6-methylthio-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 192-195 °C.
NMR (200MHz, DMSO-d6): δ 2.64(s, 3H), 4.96(d, 2H), 7.31-7.86(m, 9H), 8.26(s, 1H), 8.40(s, 1H), 9.75(t, 1H), 9.96(s, 1H).
IR (KBr): ν 3210(w), 3040(m), 2600(m), 1630(s), 1556(s), 1495(m), 1433(m), 1510(s), 1339(m), 1203(w), 1112(w), 1091(w), 1013(w), 823(w), 743(m), 704(m), 615(w) cm^{-1}.

Example 6(pp)

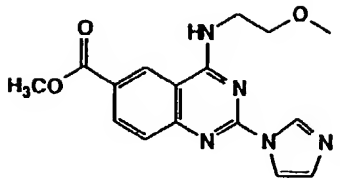
4-(3-methoxypropyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 191-194°C.
NMR (200MHz, DMSO-d6): δ 1.94(m, 2H), 3.25(s, 3H), 3.42(t, 2H), 3.69(m, 2H), 3.90(s, 3H), 7.45(m, 1H), 7.64(d, 1H), 7.86(m, 1H), 7.99(m, 1H), 8.35(m, 1H), 9.30(m, 1H), 9.88(m, 1H).
IR (KBr): ν 1641, 1603, 1587, 1573, 1529, 1421, 1382, 1253, 1111, 1027, 858 cm^{-1}.

Example 6(qq)

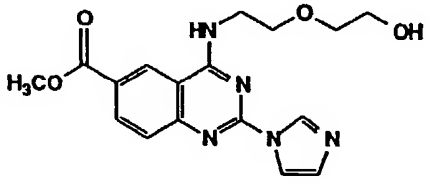
4-(2-methoxyethyl)amino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline



mp : 252-253°C.
NMR (200MHz, DMSO-d6): δ 3.32(s, 3H), 3.66(t, 2H), 3.83(t, 2H), 3.92(s, 3H), 7.13(s, 1H), 7.75(d, 1H), 7.98(s, 1H), 8.23(s, 1H), 8.63(s, 1H), 9.02(s, 1H), 9.28.
IR (KBr) : ν 3245(w), 3140(w), 2900(w), 1724(s), 1601(s), 1473(s), 1437(s), 1407(s), 1310(s), 1119(m), 1021(m), 766 cm^{-1}.

Example 6(rr)

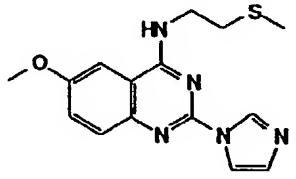
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)-quinazoline



mp : 233-235°C.
NMR (200MHz, DMSO-d6): δ 3.50(m, 4H), 3.70-3.90(m, 4H), 3.93(s, 3H), 4.60(m, 1H), 7.12(s, 1H), 7.75(d, 1H), 7.99(s, 1H), 8.25(dd, 1H), 8.63(s, 1H), 9.03(m, 1H), 9.28(m, 1H).
IR (KBr) : ν 3245(mw), 2950(w), 1730(ms), 1626(w), 1603(s), 1558(m), 1474(m), 1437(m), 1406(m), 1309(m), 1281(w), 1229(w), 1125(w), 1102(w), 1051(w) cm^{-1}.

Example 6(ss)

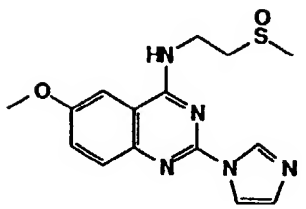
4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline



mp : 168-178°C.
NMR (200MHz, DMSO-d6): δ2.17(s, 3H), 2.89(t, 2H), 3.90(m, 2H), 3.93(s, 3H), 7.55(dd, 1 H), 7.69(d, 1H), 7.87(s, 1H), 7.97(s, 1H), 8.40(s, 1H), 9.34(t, 1H), 9.93(s, 1H).
IR (KBr) : ν 3410, 3095, 2675, 1635, 1609, 1587, 1400, 1264, 1018 cm^{-1}.

Example 6(tt)

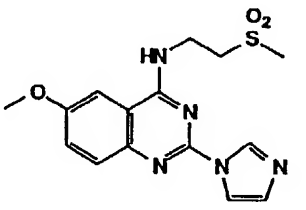
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline



mp : 238-242°C.
NMR (200MHz, DMSO-d6): δ 2.63(s, 3H), 3.10-3.70(m, 4H), 3.92(s, 3H), 7.53(dd, 1H), 7.72(d, 1H), 7.88(d, 2H), 8.48(s, 1H), 9.43(m, 1H), 10.01(s, 1H).
IR (KBr) : n 3435, 3005, 2710, 1625, 1560, 1398, 1248, 1020, 825 cm^{-1}.

Example 6(uu)

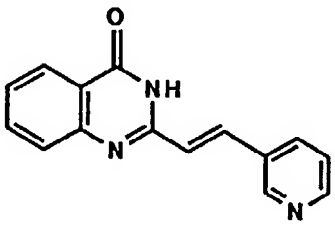
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline



mp : 245-252°C.
NMR (200MHz, DMSO-d6): δ 3.09(s, 3H), 3.61 (t, 2H), 3.92(s, 3H), 4.09(m, 2H), 7.54(dd, 1H), 7.76(d, 1H), 7.88(s, 2H), 8.45(s, 1H), 9.38(br, 1H), 9.89(s, 1H).

Reference example 15

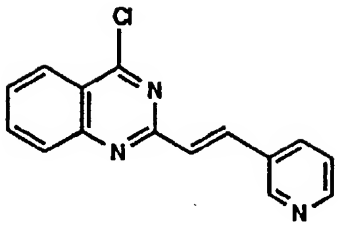
2-(2-(3-pyridyl)vinyl)quinazolin-4-one



A mixture of 2-methylquinazolin-4-one (6.1 g) and 3-pyridinecarbaldehyde (4.1 g) in acetic acid (80 mL) was heated to reflux for 20 hours. After cooling to room temperature, the precipitate was collected by filtration, washed with methanol and dried to obtain the title compound as an acetic acid salt (10.5 g).

Reference example 16

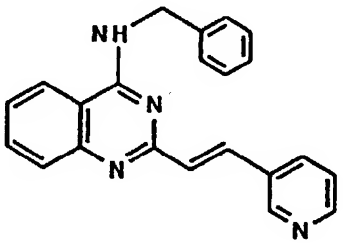
4-chloro-2-(2-(3-pyridyl)vinyl)quinazoline



A suspension of the quinazolinone compound (2.9 g, prepared in Reference example 15) in thionyl chloride (25 mL) and a few drops of dimethylformamide was heated at reflux for three hours. The mixture was then concentrated, the concentrate poured into 150 mL portions of chloroform, dried over potassium carbonate and concentrated to obtain the title compound (1.1 g) as a red oil.

Example 7

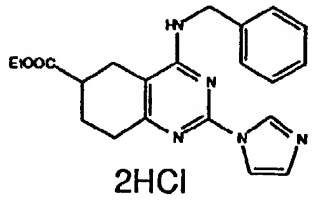
4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline



The title compound having the following physical data, was obtained by the same procedure as Example 1, by using the 4-chloro compound prepared in Reference example 16 and phenylmethylamine.
The product was purified by column chromatography.
mp : 178-179°C.
NMR ($CDCl_3$): δ 4.96 (d, 2H), 6.11 (broad, 1H), 7.30-7.55 (m, 8H), 7.70-7.81 (m, 2H), 7.99 (d, 1H), 8.34 (s, 1H), 8.36-8.45 (m, 1H), 8.55-8.58 (dd, 1H), 8.90-8.91 (d, 1H).
IR (KBr): ν 3300 (m), 1577 (s), 1528 (s), 1434 (m), 1378 (s), 763 (m), 699 (m) cm^{-1}.

Example 8

6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline and its salt



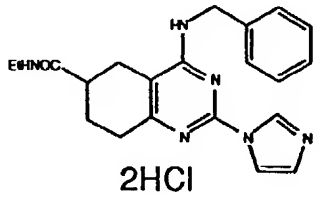
To 349 mg (1.0 mmol) of a compound prepared in example 6(t) dissolved in 20 mL of tetrahydrofuran was added 0.4 mL of thionyl chloride. Initially, a white precipitate formed, but gradually all dissolved. After stirring for 15 minutes, 20 mL of ethanol was added. After stirring an additional 15 minutes, the mixture was concentrated, the concentrate triturated in ether and collected. The solid was found to be very hygroscopic, was taken up in chloroform, treated with potassium carbonate solution, separated, dried over anhydrous magnesium sulfate and concentrated. Obtained 278 mg (0.7 mmol, 73% yield) of the desired product as a white solid (free base).
(free base)
mp : 196-198°C
NMR ($DMSO-_{d6}$): δ 1.30 (t, 3H), 1.90 (m, 1H), 2.28 (m, 1H), 2.60 (m, 2H), 2.82 (m, 3H), 4,23 (q, 2H), 4.77 (d,

2H), 5.12 (m, 1H), 7.10 (s, 1H), 7.37 (m, 5H), 7.83 (s, 1 H), 8.54 (s, 1H).
IR (KBr): 3245 (w), 1725 (ms), 1605 (s), 1532 (w), 1473 (m), 1426 (m), 1333 (w) cm^{-1}.

To a suspension of 240 mg (0.64 mmol) of the compound prepared above in 5 mL of ethanol was added 2 mL of ~10% HCl in methanol. All the material gradually dissolved. After ten minutes, the mixture was concentrated in vacuo, triturated in ether and filtered to obtain 229 mg (0.51 mmol) of the desired product.
(2HCl salt)
mp : 158-161 °C
NMR (200MHz, DMSO-d6) δ: 1.22 (t, 3H), 1.87(m, 1H), 2.14 (m, 1H), 2.55-3.00 (m, 5H), 7.79 (s, 1H), 8.23 (s, 1H), 9.77 (s, 1H).
IR (KBr) ν: 3225, 1718, 1642, 1612, 1518, 1393 cm^{-1}.

Example 8(a)

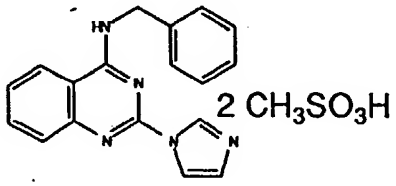
6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline dihydrochloride



By the same procedure as described in example 8, by using ethylamine instead of ethanol, the title compound having the following physical data was given.
mp : 147 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 1.04 (q,3H), 1.65-2.06 (m, 2H), 2.50-2.80 (m, 5H), 3.10 (m, 2H), 4.72 (m, 2H), 7.18-7.48 (m, 5H), 7.81 (s, 1H), 8.05 (t, 1H), 8.18 (M, 1H), 8.24 (m, 1H), 9.82 (s, 1H).
IR (KBr) ν: 3265-2580, 2365, 1653, 1613, 1576, 1540, 1449, 1390, 1352, 1144, 1060, 750, 701, 624 cm^{-1}.

Example 9

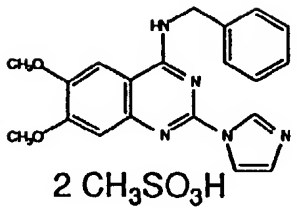
4-phenylmethylamino-2-(1-imidazolyl)quinazoline dimethanesulfonate



By the same procedure as described in Reference example 13 and 14 and example 5 and 6, by using methanesulfonic acid instead of hydrochloric acid, the title compound and the following compounds having the following physical data were given.
mp : 140-143 °C
NMR (200MHz, DMSO-d6) δ: 2.38 (s, 6H), 4.95 (m, 2H), 7.20-8.00 (m, 9H), 8.40-8.53 (m, 2H), 9.64 (t, 1H), 10.00 (s, 1H).

Example 9(a)

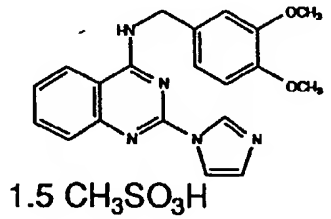
6,7-dimethoxy-4-phenylmethylamino-2-(1 -imidazolyl)quinazoline dimethanesulfonate



mp : 205 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 2.36 (s, 6H), 3.92 (s, 3H), 3.95 (s, 3H), 4.95 (m, 2H), 7.18 (d, 1H), 7.21-7.53 (m, 5H), 7.82 (s, 1H), 7.87 (m, 1H), 8.39 (m, 1H), 9.21 (t, 1H), 9.94 (m, 1H).

Example 9(b)

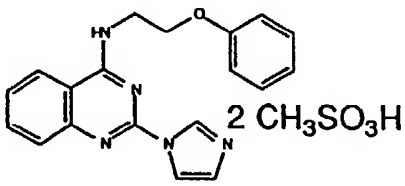
4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline 1.5 methanesulfonate



mp : 163-173 °C.
NMR (200MHz, DMSO-d6) δ: 2.34 (s, 4H), 3.73 (d, 6H), 4.88 (d, 2H), 6.02 (d, 1H), 7.03 (d, 1H), 7.16 (s, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 7.89 (m, 2H), 8.45 (d, 1H), 8.48 (s, 1H), 9.55 (t, 1H), 10.02 (s, 1H).

Example 9(c)

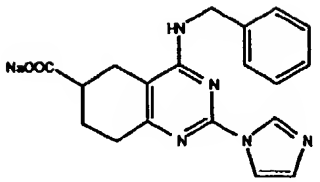
4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline dimethanesulfonate



mp : 144-161 °C
NMR (200MHz, DMSO-d6) δ: 2.39 (s, 6H), 4.12 (q, 2H), 4.34 (t, 2H), 6.97 (m, 3H), 7.28 (t, 2H), 7.63 (m, 1H), 7.80 (s, 1H), 7.91 (m, 2H), 8.45 (m, 2H), 9.30 (m, 2H), 9.97 (s, 1H).
IR (KBr) ν: 3700-2800 (broad), 1636 (s), 1211 (s) cm^{-1}.

Example 10

6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline sodium salt

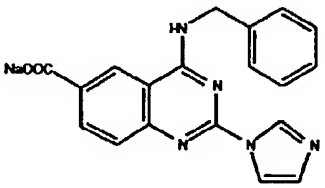


A solution of 200 mg (0.57 mmol) of a compound prepared in example 6(t) dissolved in 25 mL of tetrahydrofuran was filtered to remove dark insoluble material present. To the filtrate was added 0.25 mL (0.62 mmol) of 2.5 N sodium hydroxide solution. Some precipitate formed. The mixture was concentrated and pumped in vacuum. The concentrate was triturated in tetrahydrofuran and ether and filtered. The solid was washed with ether and filtered to obtain 190 mg (0.51 mmol) of the desired product as a white solid.
mp : 240 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 1.50-1.82 (m, 2H), 1.88-2.35 (m, 2H), 2.59 (m, 3H), 4.62 (s, 2H), 6.98 (s, 1H), 7.12-7.48 (m, 5H), 7.73 (s, 1H), 7.86 (m, 1H), 8.33 (s, 1H).

By the same procedure as described in example 10, the compound having the following physical data was given.

Example 10(a)

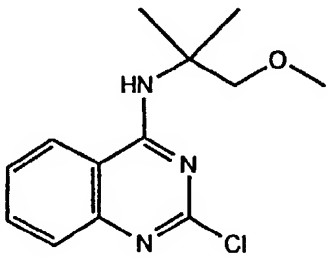
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline sodium salt



mp : >280 °C
NMR (200MHz, DMSO-d6) δ: 4.48 (d, 2H), 6.99 (s, 1H), 7.25 (m, 1H), 7.33 (m, 4H), 7.40 (d, 1 H), 7.78 (s, 1H), 7.97 (dd, 1H), 8.46 (s, 1H), 8.57 (d, 1 H), 9.11 (br, 1H).
IR (KBr) ν: 3500-3100 (br), 1620, 1559, 1472, 1399, 1307, 1224, 1056, 699 cm^{-1}.

Reference example 17

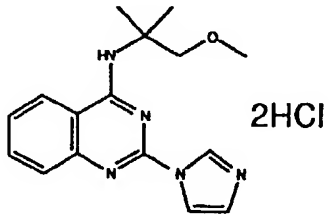
4-(1,1-dimethyl-2-methoxyethyl)amino-2-chloroquinazoline



A mixture of 2,4-dichloroquinazoline (995 mg, 5 mmol), triethylamine (0.7 ml, 5 mmol) and 1,1-dimethyl-2-methoxyethylamine (30 mL, 0.5 M methanol sol., 15 mmol) was stood at room temperature for 1 week. The reaction mixture was concentrated and partitioned between ethyl acetate and water. Organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified on 50 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (176 mg) as a white solid.
NMR ($CDCl_3$): δ 1.60 (s, 6H), 3.46 (s, 3H), 3.56 (s, 2H), 7.38-7.80 (m, 4H).

Example 11

4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



A mixture of the compound prepared in Reference example 17 (165 mg, 0.62 mmol), imidazole (169 mg, 2.48 mmol) and phenol (0.7 g) was heated at 150 °C for 40 min. After cooling, the reaction mixture was diluted with ethyl acetate, and washed with 1N KOH and brine, and dried over $MgSO_4$. The filtrate was concentrated to leave a viscous oil, which was purified on 8 g of silica gel column eluting with 50% ethyl acetate in hexane to obtain the title compound (165 mg, 90% yield) as a colorless amorphous.

(free base)

NMR ($CDCl_3$): δ 1.65 (s, 6H), 3.48 (s, 3H), 3.58 (s, 2H), 6.32 (broad, 1H), 7.17 (s, 1H), 7.40 (m, 1H), 7.62-7.81 (m, 3H), 7.97 (s, 1H), 8.67 (s, 1H).

To a solution of the compound above (160 mg, 0.54 mmol) in methanol (2mL) was added excess HCl-methanol solution (2mL). After stirring for 20 min at room temperature, the reaction mixture was concentrated. Excess HCl was evaporated with methanol (x3) to leave a white solid. Trituration with ether gave HCl salt (185 mg) as a white powder.

(HCl salt)

mp : 223-225 °C

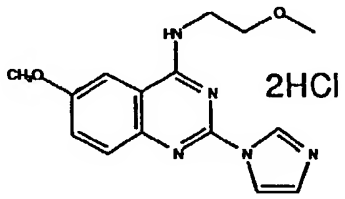
NMR (200MHz, DMSO-d6) δ: 9.80 (s, 1H), 8.59 (m, 1H), 8.34 (m, 1H), 7.84-7.96 (m, 3H), 7.78 (m, 1H), 7.60 (m, 1H), 3.78 (s, 2H), 3.29 (s, 3H), 1.57 (s, 6H).

IR (KBr) ν: 1633, 1610, 1562, 1520, 1474, 1397, 1108, 754 cm^{-1}.

By the same procedure as described in Reference example 17 and example 11, by using corresponding amine, the compounds having the following physical data were given.

Example 11 (a)

6-methoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



(HCl salt)

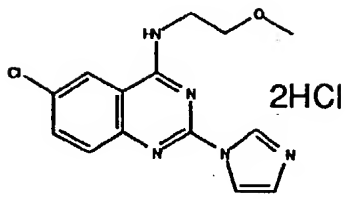
mp : 169 °C, (dec.)

NMR (200MHz, DMSO-d6) δ: 3.31, (s, 3H), 3.69 (t, 2H), 3.92 (s, 3H), 7.50 (dd, 1H), 7.88 (s, 1H), 7.97 (s, 1H), 8.42 (s, 1H), 9.21 (t, 1H), 9.99 (s, 1H).

IR (KBr) ν: 3380, 3200-2700, 1636, 1608, 1569, 1385, 1264, 1111, 1018 cm^{-1}.

Example 11 (b)

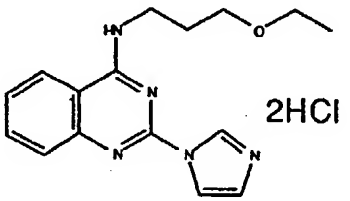
6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 200 - 206 °C, (browning)
NMR (200MHz, DMSO-d6) δ: 10.0 (s, 1H), 9.32 (m, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.85-7.96 (m, 2H), 7.77 (d, 1H), 3.90 (m, 2H), 3.66 (m, 2H), 3.32 (s, 3H).
IR (KBr) v: 1606, 1578, 1555, 1524, 1498, 1445, 1395, 1354, 1320, 1108, 1012, 876, 829 cm^{-1}.

Example 11(c)

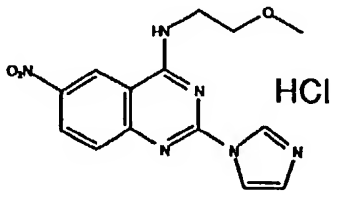
4-(3-ethoxypropyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 170-180 °C
NMR (200MHz, DMSO-d6) δ: 1.11 (t, 3H), 1.9 (qt, 2H), 3.38-3.54 (m, 4H), 3.74 (m, 2H), 7.60 (t, 1H), 7.78 (d, 1H), 7.90 (m, 2H), 8.44 (m, 2H), 9.22 (t, 1H), 9.97 (s, 1H).
IR (KBr) v: 2870-3950, 1624, 1556, 1473, 1400, 1311, 1090 cm^{-1}.

Example 11(d)

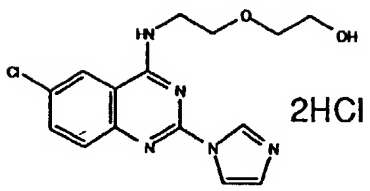
6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline hydrochloride



mp : 211 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 3.33 (s, 3H), 3.66-3.71 (m, 2H), 3.90-3.95 (m, 2H), 7.84 (m, 1H), 7.88 (d, 1H), 8.44 (m, 1H), 8.59 (m, 1H), 9.54 (m, 1H), 9.85 (bt, 1H), 9.94 (d, 1H).
IR (KBr) v: 3430, 3220-2585, 1606, 1579, 1523, 1499, 1444, 1404, 1336, 1259, 1147, 1115, 1091, 1059, 1016, 847, 825 cm^{-1}.

Example 11 (e)

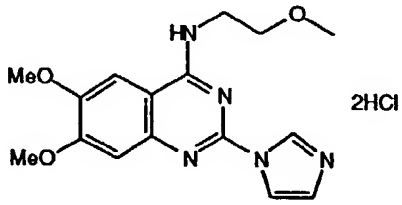
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 184-186 °C
NMR (200MHz, DMSO-d6) δ: 3.51 (s, 4H), 3.75-3.77 (m, 2H), 3.85-3.90 (m, 2H), 7.76 (d, 1H), 7.84 (m, 1H), 7.91 (dd, 1H), 8.40 (t, 1H), 8.67 (m, 1H), 9.30 (bt, 1H), 9.92 (m, 1H).
IR (KBr) ν: 3320, 3175-2825, 1602, 1574, 1497, 1439, 1398, 1343, 1118 cm^{-1}.

Example 11 (f)

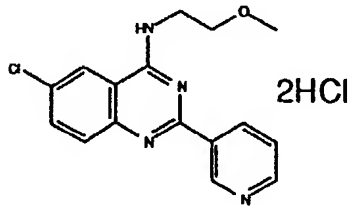
6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline dihydrochloride



mp : 249-251 °C
NMR (200MHz, DMSO-d6) δ: 3.32 (s, 3H), 3.65 (t, 2H), 3.85 (m, 2H), 3.94 (s, 6H), 7.16 (s, 1H), 7.88 (s, 2H), 8.39 (s, 1H), 8.92 (t, 1H), 9.95 (s, 1H).
IR (KBr) ν: 3425-2365, 1642, 1603, 1573, 1511, 1481, 1456, 1386, 1287, 1240, 1156, 1132, 1109, 1021, 988, 876, 770 cm^{-1}.

Example 12

6-chloro-4-(2-ethoxyethyl)amino-2-(3-pyridyl)quinazoline and its salt



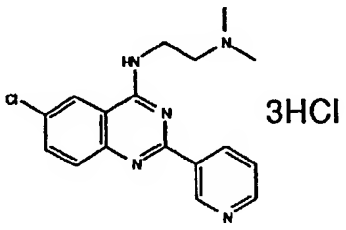
A solution of 2-(3-pyridyl)-4,6-dichloroquinazoline (1.0 g, 3.2 mmol, prepared in Reference example 5(b)) and 2-methoxyethylamine (0.53 g, 7.0 mmol) in 50 mL of ethanol was heated to reflux overnight. The solution was concentrated, taken up in chloroform and water. After some mixing, the water layer was found to be slightly acidic and was basified with sodium carbonate. The mixture was then agitated and separated. The organic layer was dried over potassium carbonate and concentrated. The concentrate was purified on silica gel column with 5% methanol in chloroform as eluent. The product obtained was combined with additional material filtered from the aqueous layer. Obtained a total of 0.35 g (1.1 mmol) of the title compound.
(free base)
mp : 210-212°C
NMR (200MHz, $DMSO-_{d6}$): δ 3.32 (s, 3H), 3.67 (t, 2H), 3.87 (qd, 2H), 7.53 (m, 1 H), 7.82 (s, 2H), 8.48 (s, 1H), 8.71 (m, 3H), 9.59 (s, 1H)
IR (KBr): ν 3250 (m), 1692 (s), 1535 (s), 1430 (w), 1412 (w), 1366 (m), 1140 (m), 823 (m) cm^{-1}.

To a mixture of 0.35 g (1.1 mmol) of the compound prepared above in 5 mL of methanol was added 0.5 mL of 10% HCl in methanol. The solution was concentrated to 1 mL, triturated in ether, filtered and dried under vacuum. Obtained 0.33 g (0.85 mmol) of the hydrochloride.
(HCl salt)
mp : 190 °C, (dec.)
NMR (200MHz, DMSO-d6) δ: 3.32 (s, 3H), 3.71 (t, 2H), 3.94 (m, 2H), 8.01 (m, 2H), 8.12 (d, 1H), 8.75 (m, 1H), 9.01 (d, 1H), 9.20 (d, 1H), 9.66 (s, 1H).
IR (KBr) ν: 3425, 2500-3050, 1633,1610,1569,1387, 1107 cm^{-1}.

By the same procedure as described in Example 12, by using corresponding amine, the compounds having the following physical data was given.

Example 12(a)

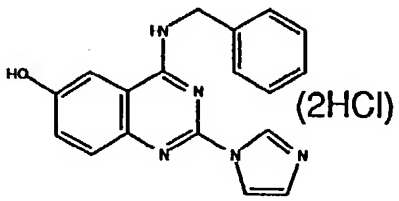
6-chloro-4-(2-dimethylaminoethyl)amino-2-(3-pyridyl)quinazoline trihydrochloride



mp = 179 °C (dec.).
NMR (200 MHz, D_2O): δ 2.96 (s, 6H), 3.51 (t, 2H), 4.02 (t, 2H), 7.57 (m, 1H), 7.70 (m, 3H), 8.68 (m, 2H), 9.14 (s, 1H).
IR (KBr) ν: 3405, 3215, 2545, 1577, 1536, 1474, 1437, 1396, 1360, 827, 721 cm^{-1}.

Example 13

6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline and its salt



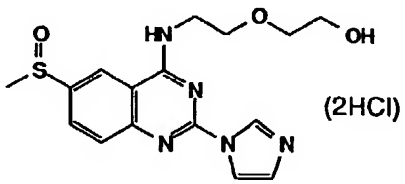
To 66 mg (0.2 mmol) of the compound prepared in Example 6(g) in 1 mL of acetic acid was added 0.8 mL (7 mmol) of 48% HBr in water. The mixture was heated below reflux for 23 hours then heated to full reflux for four hours. After cooling to room temperature, 15 mL of water was added to the solution and the precipitate was filtered and dried under vacuum. The material was purified on a preparative silica gel plate with 10% methanol in chloroform. Obtained 13 mg (41 μmol) of the desired product as a solid.
(free base)
mp : 230 °C, (dec.)
NMR (200MHz, CD3OD) δ: 4.86 (s, 2H), 7.05 (s, 1H), 7.15-7.38 (m, 4H), 7.40-7.50 (m, 3H), 7.58-7.66 (m, 1H), 7.92 (s, 1H), 8.52 (s, 1H).
IR (KBr) ν: 3370, 3030, 2365, 1749, 1710, 1653, 1596, 1559, 1523, 1488, 1465, 1407, 1376, 1291, 1244 , 1162, 1098, 1060, 911, 831 cm^{-1}.

By the same procedure as described in Example 12, the hydrochloride having the following physical data was given.
(2HCl salt)
mp : 155 °C, (dec.)

NMR (200MHz, DMSO-d6) δ: 4.92 (m, 2H), 7.22-7.77 (m, 8H), 7.86 (s, 1H), 8.38 (s, 1 H), 9.36 (m, 1H), 9.94 (s, 1H).
IR (KBr) v: 3395-2640, 2365, 1734, 1628, 1607, 1567, 1542, 1473, 1361, 1353, 1289, 1260, 1201, 1107, 1015, 835, 753, 702 cm^{-1}.

Example 14

4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline and its dihydrochloride



To 1.38 g of the compound prepared in example 6(mm) dissolved in 10 mL of acetic acid was added 4 mL of 30% hydrogen peroxide. The reaction was monitored by TLC. After stirring for 1/2 hour, the mixture was poured into 15 g of 50% w/w sodium hydroxide and ice. The resulting mixture was extracted four times with chloroform, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and collected to obtain 1.26 g of the desired product as a white solid.

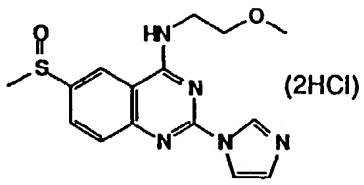
To 400 mg of the compound prepared above in 10 ml of methanol was added 1 mL of 10% HCl in methanol. After ten minutes, the mixture was concentrated, triturated in ether and the solid collected. Obtained 441 mg of the desired product as a dihyrochloride salt.

(free base)
mp : 144-147°C
NMR (200MHz, DMSO-d6): d 2.85(s, 3H), 3.50(m, 4H), 3.70-3.90(m, 4H), 4.59(m, 1H), 7.11(s, 1H), 7.82(m, 1H), 7.98(s, 1H), 8.02(m, 1H), 8.62(s, 1H), 8.67(m, 1H), 9.14(t, 1H).
(2HCl salt)
mp : 190-192°C
NMR (200MHz, DMSO-d6): d 2.89(s, 3H), 3.51(s, 4H), 3.76(m, 2H), 3.89(m, 2H), 7.90(m, 2H), 8.14(m, 1H), 8.45(m, 1H), 8.89(m, 1H), 9.62(t, 1H), 10.10(m, 1H).

By the same procedure as described in Example 14, by using corresponding thioether, the compounds having the following physical data were given.

Example 14(a)

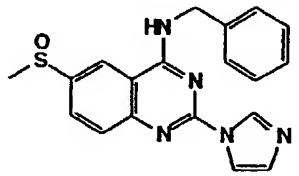
4-(2-methoxyethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline and its dihydrochloride



(free base)
mp : 170-173°C
NMR (200MHz, DMSO-d6): d 2.85(s, 3H), 3.32(s, 3H), 3.69(m, 2H), 3.83(m, 2H), 7.12(s, 1H), 7.77-8.10(m, 2H), 7.98(s, 1H), 8.68(s, 1H), 9.16(s, 1H).
(2HCl salt)
mp : 191-193°C
NMR (200MHz, DMSO-d6): d 2.89(s, 3H), 3.31(s, 3H), 3.67(m, 2H), 3.89(m, 2H), 7.86-8.18(m, 3H), 8.45(m, 1H), 8.89(m, 1H), 9.63(t, 1H), 10.05(m, 1H).

Example 14(b)

6-methylsulfinyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline dihydrochloride

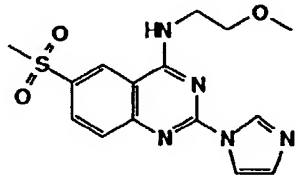


2HCl

mp : 167-170°C.
NMR (200MHz, DMSO-d6): δ 2.87(s, 3H), 4.96(d, 2H), 7.32-7.53(m, 5H), 7.87(d, 1H), 7.93(s, 1H), 8.15(s, 1H), 8.42(s, 1H), 8.86(s, 1H),10.01(s, 1H), 10.10(t, 1H).
IR (KBr): ν 3370(w), 3220(w), 3060(m), 2825(m), 1617(s), 1577(s), 1541(m), 1497(w), 1444(m), 1396(s), 1355(w), 1014(m), 836(w), 788(w), 702(w) cm^{-1}.

Example 15

4-(2-methoxyethyl)amino-6-methylsulfonyl-2-(1-imidazolyl)quinazoline hydrochloride



HCl

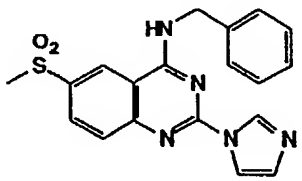
To 0.63 g of the compound prepared in example 6(11) (free base) in 7 mL of acetic acid was added 3 ml of 30% hydrogen peroxide solution and the mixture was stirred at room temperature for 17 hour. The mixture was then poured into a solution of 50% w/w sodium hydroxide in ice. The resulting mixture was extracted twice with 70 mL portions of chloroform, dried over anhydrous magnesium sulfate and concentrated. The concentrate was triturated in ether and the solid collected to obtain 0.36 g of the desired product as a white powder.

To a suspension of 300 mg of the compound above in 15 mL of methanol was added 1 mL of 10% HCl in methanol. The mixture become clear then a precipitate formed. The mixture was concentrated to approximately 5mL, diluted with ether and filtered to obtain 319 mg of the desired product as a white solid.
(free base)
mp : 241-243 °C
(HCl salt)
mp : 226-228°C
NMR (200MHz, DMSO-d6): d 3.32(s, 3H), 3.36(s, 3H), 3.67(m, 2H), 3.93(m, 2H), 7.81(s, 1H), 7.93(m, 1H), 8.30(m, 1H), 8.42(s, 1H), 9.16(m, 1H), 9.72(t, 1H), 9.92(s, 1H).

By the same procedure as described in Example 15, the below compound having the following physical data was given.

Example 15(a)

6-methylsulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline hydrochloride

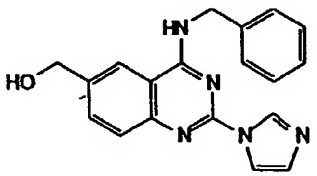


HCl

mp : 125-130°C.
NMR (200MHz, DMSO-d6): δ 3.34(s 3H), 4.97(d, 2H), 7.31-7.50(m, 5H), 7.85(s, 1H), 7.93(d, 1H), 8.32(d, 1H), 8.44(s, 1H), 9.14(s, 1H), 9.98(s, 1H), 10.12(t, 1H).
IR (KBr): ν 3230(s), 3040(s), 2705(s), 2370(m), 1616(s), 1572(s), 1524(s), 1497(m), 1399(s), 1326(s), 1258(m), 1204(w), 1147(s), 1008(m), 834(w), 783(s), 730(w), 620(w), 535(m) cm^{-1}.

Example 16

6-hydroxymethyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline

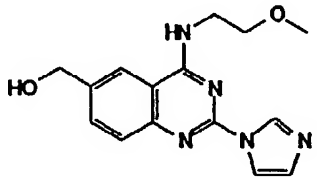


To a suspension of 0.68 g of the compound prepared in example 5(e) in 50 mL of anhydrous tetrahydrofuran was added 2 mL of 2M lithium borohydride in tetrahydrofuran. The reaction mixture was heated at reflux for two days. The mixture was then concentrated, diluted with water and the basic solution was acidified with 1N hydrochloric acid. The resulting solution was then basified with potassium carbonate, filtered and the solid washed with water and allowed to dry. The solid material was purified on silica gel column eluting with 5% methanol in chloroform. Obtained 85 mg of the desired product.
mp : 173 °C (dec.).
NMR (200MHz, DMSO-d6): δ 4.67(d, 1 H), 4.90(d, 1H), 5.47(t, 1H), 7.23(m, 1H), 7.25-7.51(m, 5H), 7.67-7.85(m, 2H), 8.12(m, 1H), 8.34(m, 1H), 8.91(s, 1H), 9.51(t, 1H).
IR (KBr): ν 3445(mw), 2365(mw), 1599(s), 1559(m), 1505(mw), 1444(w), 1410(m), 1340(w), 1161(w), 1073(w) cm^{-1}.

By the same procedure as described in Example 16, the below compounds having the following physical data were given.

Example 16(a)

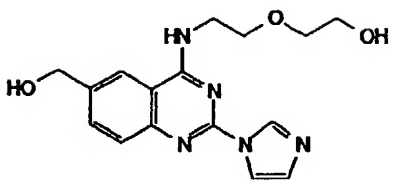
4-(2-methoxyethyl)amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline



mp : 165-168°C.
NMR (200MHz, DMSO-d6): δ 3.35(s, 3H), 3.68(t, 2H), 3.80(t, 2H), 4.65(d, 2H), 5.45(t, 1H), 7.12(s, 1H), 7.68(m, 2H), 7.99(s, 1H), 8.27(s, 1H), 8.62(s, 1H), 8.83(s, 1H).
IR (KBr) : ν 3370(m), 1597(s), 1559(m), 1474(m), 1409(m) cm^{-1}.

Example 16(b)

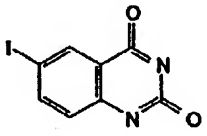
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline



mp : 183°C.
NMR (200MHz, DMSO-d6): δ 3.48(s, 4H), 3.76(m, 4H), 4.62(d, 2H), 5.44(t, 1H), 7.10(s, 1H), 7.62-7.80(m, 2H), 7.97(s, 1H), 8.27(s, 1H), 8.60(s, 1H), 8.82(bs, 1H).
IR (KBr) : ν 3311(mw), 3156(w), 1597(s), 1558(w), 1487(w), 1438(w), 1408(ms), 1052(w) cm^{-1}.

Reference example 18

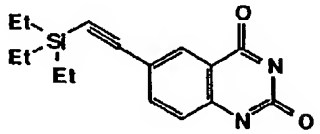
6-iodoquinazolin-2,4-dione



To a mixture of 25.36 g of 2-amino-5-iodobenzoic acid in 250 ml of water and 90 mL of THF was added 7.40 g of glacial acetic acid and stirred at room temperature. Then was added 7.82 g of potassium cyanate in water dropwise. Left to overnight. Added another 5.47 g of potassium cyanate. Stirred overnight. A total of 160 g of NaOH pellets were added portionwise, keeping the mixture cool in ice-water bath. The mixture was stirred at room temperature overnight. The mixture was cooled in a refrigerator and the precipitate filtered through a sintered glass funnel. The precipitate was then dissolved in water and acidified with 4N HCl. The precipitate was collected by filtration. The solid was dried in a vacuum oven to yield 25.44 g of the title compound.

Reference example 19

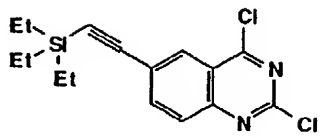
6-(2-triethylsilylethylnyl)quinazolin-2,4-dione



In a flusk was placed 0.544 g of triphenylphosphine, 0.184 g of palladium chloride, and 5 mL of diethylamine. Stirred under a nitrogen atmosphere. To the resulting yellow mixture was added 75 mL of diethylamine, followed by 10.02 g of the compound prepared in reference example 18. Then added 19.8 mg of cuprous iodine to the purple suspension. Turned gray after 10 minutes. After 0.5 hr added 5.36 g of triethylsilyl acetylene and stirred at room temperature. After 3 hrs the solution turned purple. After another 1.5 hrs. the solution turned brown. Left to stir overnight. Monitored reaction by TLC. Removed the solvent under reduced pressure at 40 °C and added water. Acidified with 1N- HCl. The precipitated solid was collected by filtration, washed with water, and dried in a vacuum oven. The solid was then passed through a silica gel column, eluting with THF. After drying yielded 10.22 g of the title compound having the following physical data.
NMR (200 MHz, DMSO-d_6): δ 0.65(dd, 6H), 0.93(dd, 9H), 7.15(d, 1H), 7.69(d, 1H), 11.38(br, 2H).

Reference example 20

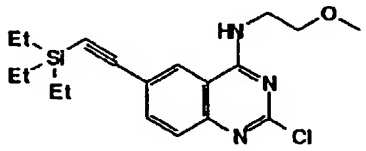
2,4-dichloro-6-(2-triethylsilylethylnyl)quinazoline



To 5.09 g of the compound prepared in reference example 19, was added 25 mL of $POCl_3$ and warmed. Then added 1.03 g of N,N-dimethylaniline and heated to reflux. After 3.5 hrs, the excess $POCl_3$ was removed under reduced pressure and the residue diluted in chloroform and poured slowly over ice. The organic layer was collected and the solvent removed. The residue was passed through a silica gel column using 20% EtOAc/hexane as a solvent. Yielded 1.4 g of the product having the following physical data.
NMR (200 MHz, CDCl3): δ 0.72(6H), 1.00(9H), 7.98(d, 1H), 8.33(s, 1H).

Reference example 21

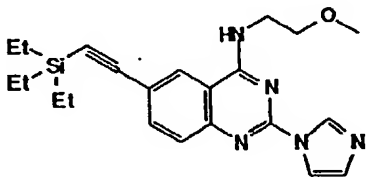
2-chloro-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline



To 1.4 g of the compound prepared in reference example 20 in 20 mL of chloroform was added 2-methoxyethylamine and stirred at room temperature for 1.5 hr. Then added 4.2 ml of 1N-NaOH and heated to reflux. Left to reflux overnight. The solvent was removed under reduced pressure and the residue taken up in chloroform and water. The organic layer was collected and dried over anhydrous potassium carbonate. Removal of solvent under reduced pressure yielded 1.44 g of the title compound.
NMR (200 MHz, $CDCl_3$): δ 0.73 (m, 6H), 1.07(m, 9H), 3.45(s, 3H), 3.69(t, 2H), 3.88(dd, 2H), 6.32(br, 1H), 7.69(d, 1H), 7.78(dd, 1 H), 7.80(s, 1 H).

Example 17

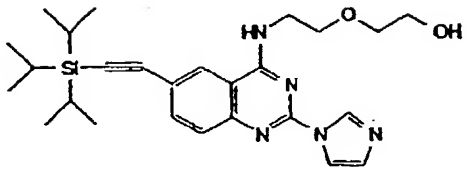
2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline



To 1.32 g of the compound prepared in reference example 21 in 5 mL of ethanol was added excess imidazole (0.93 g) and heated in an oil bath to 115 °C. After 1.5 hrs. removed from heat and diluted in chloroform and washed with 1N-NaOH, collected the organic layer and washed with water. The organic layer was extracted and dried over anhydrous potassium carbonate. Removal or solvent yielded 1.33 g of the title compound. mp : 158-160 °C.
NMR (200 MHz, DMSO-d_6): δ 0.70(q, 6H), 1.05(t, 9H), 3.30(s, 3H), 3.64(t, 2H), 3.81(dd, 2H), 7.10(s, 1H), 7.65(d, 1H), 7.78(dd, 1H), 7.96(s, 1H), 8.01(s, 1 H), 8.60(s, 1H), 8.95(br, 1H).
By the same procedures as described in reference examples 18, 19, 20 and 21, and example 17, the following compound was obtained.

Example 17(a)

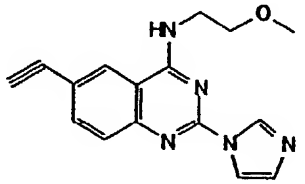
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilyl-ethynyl)quinazoline



mp: 155-156 °C;
NMR (200MHz, $CDCl_3$): δ 1.09 (s, 3H), 1.16 (s, 18H), 2.28 (br, 1H), 3.70 (m, 2H). 3.84 (dd, 4H), 3.95 (t, 2H), 6.65 (br, 1H), 7.14 (s, 1H), 7.68 (d, 1H), 7.75 (dd, 1H), 7.87 (s, 1H), 7.93 (s, 1H), 8.65 (s, 1H).

Example 18

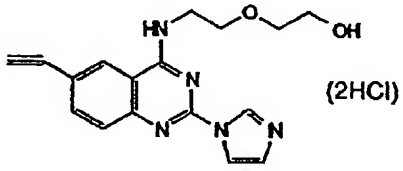
6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline



To 1.35 g of the compound prepared in example 17 in 20 mL of THF was added 3.3 mL of tetrabutylammonium fluoride (1M in THF). Stirred at room temperature for 1.5 hrs. The excess THF was removed under reduced pressure and the residue taken up in chloroform and water. The insoluble precipitate was collected by filtration. Yielded 0.83 g of the title compound.
NMR (200MHz, DMSO-d6): δ .3.33(s, 1H), 3.66(m, 2H), 3.83(m, 2H), 4.34(s, 1H), 7.11(s, 1H), 7.65(d, 1H), 7.82(dd, 1H), 7.96(s, 1H), 8.57(d, 1H), 8.62(s, 1H), 8.90(broad, 1H).
IR (KBr): v 3290(s), 2945(m), 1606(s), 1559(s), 1451(s), 1352(s), 1106(s), 835(s) cm^{-1}.
By the same procedure as described in example 18, the following compound was given.

Example 18(a)

2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline and its salt

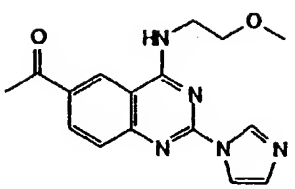


(2HCl)

(free base)
mp : 166-167°C;
NMR (200MHz, DMSO-d6): δ 3.50 (s, 4H), 3.78 (m, 4H), 4.35 (s, 1H), 4.59 (t, 1H), 7.10 (s, 1H), 7.65 (d, 1H), 7.80 (dd, 1H), 7.97 (s, 1H), 8.55 (d, 1H), 8.61 (s, 1H), 8.90 (br, 1H).
(HCl salt)
mp : 178 °C;
NMR (200MHz, DMSO-d6): δ 3.51 (s, 4H), 3.87 (m, 2H), 4.44 (s, 1H), 7.73 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.40 (s, 1H), 8.67 (s, 1H), 9.25 (br, 1H).

Example 19

6-acetyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline



To 0.541 g of the compound prepared in example 18 in 10 ml of acetic acid was added 0.7 mL of 10% H_2SO_4 and 0.10 g of mercury II sulfate and heated to reflux. After 2 hours removed from heat and basified. The yellow precipitate was filtered. The solid was washed with THF. Removed the solvent under reduced pressure and titrated the residue in 50 % ether/pentane. The solid was collected by filtration. Yielded 0.063 g of the desired product.

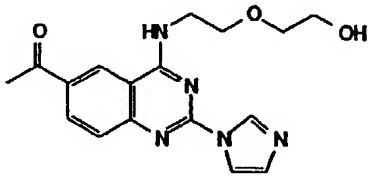
mp : 208-210 °C.

NMR (200MHz, $CDCl_3$): δ 2.64(s, 1H), 3.49(s, 3H), 3.79(t, 2H), 3.95(q, 2H), 7.00(broad, 1H), 7.16(t, 1H), 7.74(d, 1H), 7.95(t, 1H), 8.17(dd, 1H), 8.42(d, 1H), 8.67(t, 1H).

By the same procedure as described in Example 19, the below compound having the following physical data was given.

Example 19(a)

4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline



mp : 164-166°C.

NMR (200MHz, DMSO-d6): δ 2.69(s, 3H), 3.51 (s, 4H), 3.76(m, 2H), 3.84(t, 2H), 4.60(br, 1H), 7.12(s, 1H), 7.73(d, 1H), 7.98(s, 1H), 8.27(dd, 1H), 8.64(s, 1H), 9.00(s, 1H), 9.25(br, 1H).

IR (KBr) : n 3350,1671,1623, 1593, 1558, 1474, 1447, 1418, 1365, 1307, 1270, 1111, 1051 cm^{-1}.

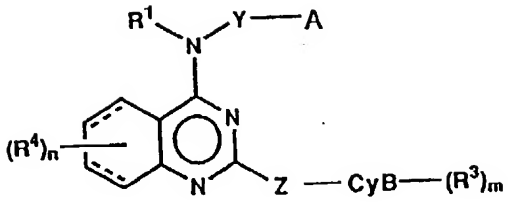
Formulation Example 1

The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

4-phenylmethylamino-2-(3-pyridyl)quinazoline	— 5.0 g
cellulose calcium glycolate (disintegrating agent)	— 0.2 g
magnesium stearate (lubricating agent)	— 0.1 g
micro crystalline cellulose	— 4.7 g

Claims

1. A quinazoline derivative of the formula:



(I)

wherein — represents a single or double bond;
R^1 is hydrogen or C_{1-4} alkyl;
Y is a single bond or C_{1-6} alkylene;
A is
(i) -CyA-$(R^2)_1$,
(ii) -O-R^0 or -$S(O)_p$-R^0, or
(iii) -$NR^{16}R^{17}$;
in which R^0 is hydrogen, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl or -CyA-$(R^2)_1$;
R^{16} and R^{17} independently are hydrogen or C_{1-4} alkyl;
p is 0-2;
CyA is
(1) a 3-7 membered, saturated or unsaturated carbocycle,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,
(6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
(7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;
R^2 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^5$, in which R^5 is hydrogen or C_{1-4} alkyl, (5) -NR^6R^7, in which R^6 and R^7 independently are hydrogen or C_{1-4} alkyl, (6) -$SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;
Z is a single bond, methylene, ethylene, vinylene or ethynylene;
CyB is
(1) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
R^3 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl;
R^4 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^8$, in which R^8 is hydrogen or C_{1-4} alkyl, (5) -NR^9R^{10}, in which R^9 is hydrogen, C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{10} is hydrogen or C_{1-4} alkyl, (6) -$NHCOR^{11}$, in which R^{11} is C_{1-4} alkyl, (7) -$NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$ in which R^9 and R^{10} are as hereinbefore defined, (9) -$OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -$SO_2N{=}CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl, (16) -$CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{15} is C_{1-4} alkyl or (17) C_{1-4} alkylthio, (18) C_{1-4} alkylsulfinyl, (19) C_{1-4} alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl)silylethynyl or (23) acetyl;
and l, m and n independently are 1 or 2;
with the proviso that
(1) CyA-$(R^2)_1$ does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,
(2) CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,
(3) CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and

(4) Y is not a single bond when A is (ii) -O-R^0 or -$S(O)_p$-R^0 or (iii) -$NR^{16}R^{17}$;
or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

2. A compound according to claim 1, wherein CyB is a pyridine ring, an imidazole ring, a triazole or pyrrole ring, or a furan or thiophene ring.

3. A compound according to claim 1 or 2, wherein CyA is a benzene ring, a cyclopropyl ring, a cyclohexyl ring, a pyridine ring, a pyrrole or isoxazole ring, a thiophene ring, or a furan, tetrahydrofuran or pyran ring.

4. A compound according to claim 1, 2 or 3 wherein A is OH, -O-C_{1-4} alkyl, -O-C_{1-4} alkyl-OH, -$S(O)_p$-C_{1-4} alkyl, or -$NR^{16}R^{17}$.

5. A compound according to any one of claims 1 to 4, wherein Y is a single bond, methylene or ethylene.

6. A compound according to any one of claims 1 to 5, wherein Z is a single bond, methylene, or vinylene.

7. A compound according to any one of the preceding claims, which is:
4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-méthanesulfonylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(4-pyridyl)quinazoline,

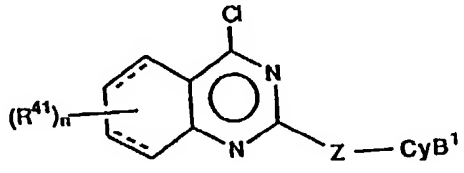
4-phenylmethylamino-6-sulfamoyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,
4-phenylamino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
4-phenylethylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-pyridyl)quinazoline,
4-phenylmethylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)ethyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,
6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(cyclohexylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-azepinylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
4-((1-methyl-2-pyrrolyl)methyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline.
4-(2-furylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-tetrahydrofuranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(4-tetrahdyropyranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-thienylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(3-ethoxypropyl)amino-2-(1-imidazolyl)quinazoline,
6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-ethoxyethyl)amino-2-(3-pyridyl)quinazoline,
6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methoxy-2-(2-methyl-1-imidazolyl)quinazoline,
4-(2-hydroxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfonyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline,
2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,
6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
6-ethynyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,

4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,
4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbony1-2-(-imidazolyl)-quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline,
4-(2-methoxyethyl)amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-G-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-(3-methoxypropyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropyl- silylethynyl)-quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,
4-phenylmethylamino-6-methyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,
4-phenylmethylamino-2-(2-methyl-1 -imidazolyl)quinazoline,
6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline,
6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,
6-chloro-4-(3-carboxyphenyl)amino-2-(1 -imidazolylmethyl)quinazoline,
6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(2-phenylethyl)amino-2-(1 -imidazolyl)quinazoline,
4-cyclohexylmethylamino-2-(1 -imidazolyl)quinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(2-azepinyl)quinazoline,
4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,
4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,
4-phenylmethylamino-2-(2-triazinyl)quinazoline,

4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,
4-phenylmethylamino-2-(1-triazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline
4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
6-hydroxymethyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline
6-methylthio-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-thienyl)quinazoline,
4-phenylmethylamino-2-(2-furyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

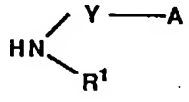
8. A process for the preparation of a 4-aminoquinazoline derivative of formula (I) as defined in claim 1, comprising:

(a) reacting a compound of the formula:



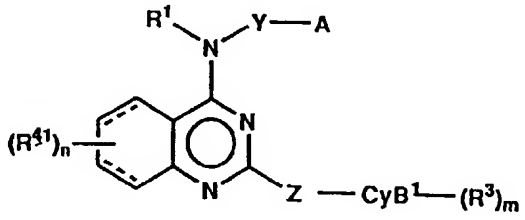
(V)

wherein R^{41} is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^8$ wherein R^8 is hydrogen or C_{1-4} alkyl, (5) -NR^9R^{10} in which R^9 and R^{10} are as hereinbefore defined, provided that R^9 and R^{10} are not both hydrogen, (6) $SO_2NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C_{1-4} alkylthio, (12) tri(C_{1-4} alkyl)silylethynyl, (13) -SO_2N=$CHNR^{12}R^{13}$, in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl or (14) -$CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{15} is C_{1-4} alkyl, CyB^1 is as defined in claim 1 for CyB, provided that CyB^1 bonds to Z through a carbon atom in the CyB^1 ring, and the other symbols are as defined in claim 1, with a compound of the formula:



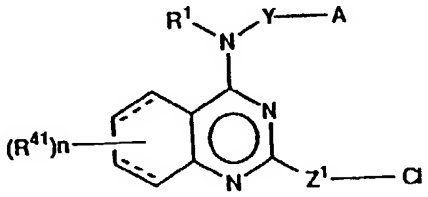
(IX)

wherein all the symbols are as defined in claim 1, to give a compound of the formula (IA):



(IA)

wherein R^{41} and CyB^1 are as defined above and the other symbols are as defined in claim 1;
(b) reacting a compound of the formula:

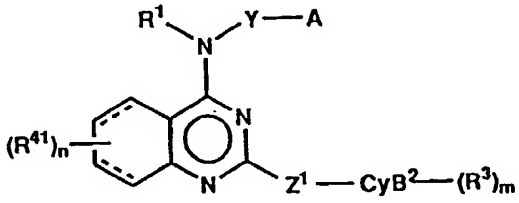


(XII)

wherein R^{41} is as defined above, Z^1 is a single bond or methylene, and the other symbols are as defined in claim 1, with a compound of the formula:

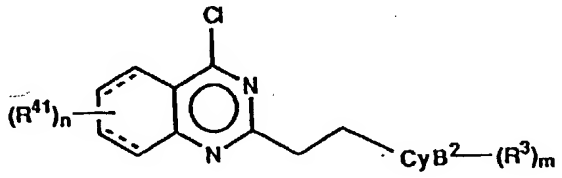
$$H\text{-}CyB^2\text{-}(R^3)_m \qquad (XVI)$$

wherein CyB^2 is as defined in claim 1 for CyB, provided that CyB^2 bonds to Z^1 through a nitrogen atom in the CyB^2 ring, and the other symbols are as defined in claim 1, to give a compound of the formula (IB):



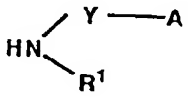
(IB)

wherein R^{41}, Z and CyB^2 are as defined above and the other symbols are as defined in claim 1; or
(c) reacting a compound of the formula:



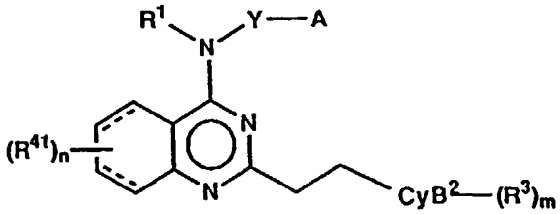
(XIX)

wherein R^{41} and CyB^2 are as defined above and the other symbols are as defined in claim 1 with a compound of the formula:



(IX)

wherein all the symbols are as defined in claim 1, to give a compound of the formula (IC):



(IC)

wherein R^{41} and CyB^2 are as defined above and the other symbols are as defined in claim 1; and optionally converting the compound of formula (I) thus obtained into another compound of formula (I).

9. A pharmaceutical composition for the treatment of mammals, including humans, comprising as active ingredient, an effective amount of a compound of the formula (I), a pharmaceutically acceptable salt thereof or a hydrate thereof in association with a pharmaceutically acceptable carrier or coating.

10. A compound of the formula (I) as defined in claim 1, a pharmaceutically acceptable salt thereof or a hydrate thereof, for use as a medicament in the treatment of mammals.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 5557

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	EP-A-0 135 975 (AKZO) * page 1 - page 13 *	1,2,8-10	C07D401/04 C07D401/06 C07D405/04
A	GB-A-2 002 746 (GIST-BROCADES) * the whole document *	1,2,8-10	C07D409/04 C07D413/14 C07D401/14
D,A	CH-A-578 556 (SANDOZ) * page 1 - page 4 *	1,8-10	C07D409/14 A61K31/505
A	FR-A-2 310 756 (SANDOZ) * the whole document *	1,2,8-10	
A	FR-A-2 102 221 (SQUIBB & SONS) * page 1 - page 11 *	1,2,8-10	
A	FR-A-2 081 456 (THE NORWICH PHARMACAL COMPANY) * page 1 - page 8 *	1,2,8-10	
A	FR-A-1 460 221 (THE NORWICH PHARMACAL COMPANY) * page 1 - page 5 *	1,2,8-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5) C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 October 1993	FRANCOIS, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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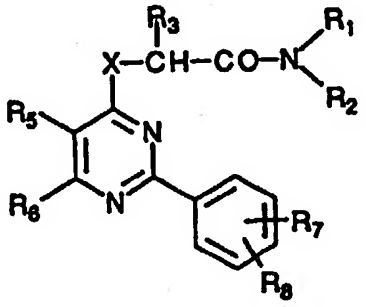
(54) ACETAMIDE DERIVATIVES, PROCESS FOR PRODUCING THE SAME, AND MEDICINAL COMPOSITION CONTAINING THE SAME

(57) Acetamide derivatives represented by general formula (I) and physiologically acceptable acid-addition salts thereof, wherein X represents -O- or -NR_4; R_1 represents H, lower alkyl, lower alkenyl or cycloalkyl(lower)alkyl; R_2 represents lower alkyl, cycloalkyl, optionally substituted phenyl, etc.; R_3 represents H, lower alkyl or hydroxy(lower)alkyl; R_4 represents H, lower alkyl, etc.; R_5 represents H, lower alkyl, lower alkenyl, hydroxy(lower)alkyl, etc.; R_6 represents H, lower alkyl, CF_3 or optionally substituted phenyl, or R_5 and R_6 together form -$(CH_2)_n$-; R_7 represents H, halogeno, lower alkyl, lower alkoxy, CF_3, OH, NH_2, etc.; and R_8 represents H, halogeno, lower alkyl or lower alkoxy. The compounds act selectively on the peripheral $BZ_{\omega 3}$ receptor and exhibit excellent pharmocological effects, which makes them useful as a remedy and preventive for central diseases, for example, diseases associated with anxiety, depression and epilepsy, etc.



(I)

EP 0 826 673 A1

Description

TECHNICAL FIELD

The present invention relates to a novel acetamide derivative selectively acting on the peripheral-type benzodiazepine receptors, more particularly, an acetamide derivative having 2-phenyl-4-pyrimidinylamino moiety or 2-phenyl-4-pyrimidinyloxy moiety, a process for preparing the same, and a pharmaceutical composition containing the same.

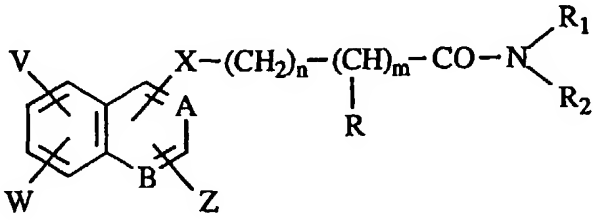
BACKGROUND ART

In the central nervous system of the mammals, including human, there are three kinds of benzodiazepine (hereinafter, occasionally referred to as BZ) recognition sites, and each is named as central-type (ω_1, ω_2) benzodiazepine receptors and a peripheral-type (ω_3) benzodiazepine receptor, respectively (hereinafter, occasionally referred to as BZω_1-receptor, BZω_2-receptor and BZω_3-receptor, respectively). Among them, the peripheral-type BZ-receptor unevenly distributes in the peripheral tissues or organs such as kidney, liver, heart, etc., but it especially distributes with high density in the cells of the endocrinium organs such as adrenal glands, testicles, etc., or in the cells deeply participating in the inflammation-immune system in whole body such as mast cells, lymphocytes, macrophages, blood platelets, etc., so that the physiological roles of the peripheral-type BZ-receptor have recently been drawing attention. On the other hand, the peripheral-type BZ-receptor is present a lot in the mitochondrial membrane of glial cells in the brain, and it participates in cholesterol influx into the mitochondrial membrane, and hence, it is thought to act on the biosynthesis pathway of cholesterol into neurosteroids such as allopregnanolone, allotetrahydrodeoxycorticosterone (THDOC), etc. via pregnenolone. Thus, it is considered that stimulation of the peripheral-type BZ-receptor accelerates the synthesis of neurosteroids in the brain which affect the choride ion channel gating process by binding to the neurosteroid-specific recognition site on the γ-aminobutyric acid-A-receptor (hereinafter, occasionally referred to as $GABA_A$-receptor) [cf. Romeo, E., et al., J. Pharmacol. Exp. Ther., 262, 971-978 (1992)].

A compound having a non-BZ nucleus and selectively showing an affinity for the peripheral-type BZ-receptor has been disclosed in Japanese Patent First Publication (Kokai) No. 201756/1983 (EP-A-94271), and since then, various compounds are disclosed in many literatures including patent applications. However, there is no compound which has actually been used as a medicament.

As a compound having a non-BZ nucleus and selectively showing an affinity for the peripheral-type BZ-receptors, in addition to the above, there have been known the compounds disclosed in Japanese Patent First Publication (Kokai) Nos. 5946/1987 and 32058/1990.

Japanese Patent First Publication (Kokai) No. 5946/1987 (EP-A-205375, USP 4788199) discloses amide compounds of the following formula, which are bound to the peripheral-type BZ-receptor, and are useful as anxiolytics, anticonvulsants and antiangina agents, and for the treatment of immuno-deficiency syndrome.

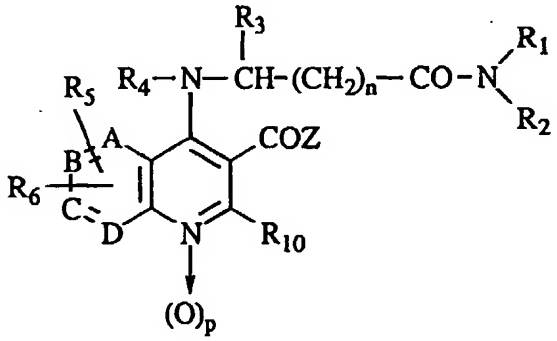


wherein A is a nitrogen atom or =CH—; B is a nitrogen atom or =CH—; V and W are the same or different and each a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group both having 1 to 3 carbon atom, etc.; Z is bound in the ortho- or para-position with respect to the B, and is a phenyl group, a thienyl group, a pyridyl group, or a phenyl group substituted by 1 to 2 groups selected from a halogen atom, an alkyl group or an alkoxy group both having 1 to 4 carbon atoms, trifluoromethyl group and a nitro group; a chain of $—X—(CH_2)_n—(CHR)_m—CONR_1R_2$ is bound in the ortho- or para-position with respect to the B; R is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms; R_1 and R_2 are the same or different and each a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, a phenyl group, a phenylalkyl group or a cycloalkylalkyl group wherein the alkyl moiety has 1 to 3 carbon atoms and the cycloalkyl moiety has 3 to 6 carbon atoms, or an alkenyl group having 3 to 6 carbon atoms wherein the double bond is not located at the 1,2-position with respect to the nitrogen atom, and R_1 and R_2 may combine together with the nitrogen atom to which they are

attached to form pyrrolidine, piperidine, morpholine or thiomorpholine ring; X is —CHR_3—, —NR_4—, —SO—, —SO_2—, an oxygen atom or a sulfur atom; R_3 is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms; R_4 is an alkyl group having 1 to 3 carbon atoms; m is 0 or 1; and n is 0, 1 or 2,

provided that when X is —SO—, —SO_2— or —NR_4—, the total number of m + n should be at least 1, and that when both of A and B are a nitrogen atom and Z is at the para-position with respect to the B, X should not be —CHR_3—, and that when A is =CH—, B is a nitrogen atom, Z is in the ortho-position with respect to the B, X is an oxygen atom and R is a hydrogen atom, the total number of m + n is other than 1, and excluding 2-phenyl-4-quinolyl-N,N-dimethylcarbamate.

Japanese Patent First Publication (Kokai) No. 32058/1990 (EP-A-346208, USP 5026711) discloses that 4-amino-3-carboxyquinoline compounds of the following formula show an affinity for the peripheral-type BZ-receptor both *in vivo* and *in vitro*, and can be used in the prophylaxis or treatment of human cardiovascular diseases, or as an antiallergic agent, or in the prophylaxis or treatment of infectious diseases, or in the treatment of anxiety.



wherein R_1 and R_2 are each a hydrogen atom, a C_1-C_6 alkyl group, or a C_2-C_6 alkenyl group, a phenyl group or a benzyl group, or R_1 and R_2 may combine together with the nitrogen atom to which they are attached to form a C_4-C_8 saturated heterocyclic group; R_3 is a hydrogen atom, a C_1-C_6 alkyl group, a phenyl group or a C_7-C_9 phenylalkyl group; R_4 is a hydrogen atom or a C_1-C_4 alkyl group; R_5 and R_6 are each a hydrogen atom, a halogen atom, a C_1-C_3 alkyl or alkoxy group, a nitro group, or a trifluoromethyl group, or combine together to form a methylenedioxy group; Z is OR_7 (R_7 is a hydrogen atom or a C_1-C_6 alkyl group), NR_8R_9 (R_8 and R_9 are each a hydrogen atom, a C_1-C_4 alkyl group, a phenyl group or a benzyl group), a C_1-C_4 alkyl group, a benzyl group, a C_4-C_6 aryl group which may optionally have a heteroatom; R_{10} is a hydrogen atom, a C_1-C_4 alkyl group or a phenyl group (provided that when Z is not a benzyl group or an aryl group, R_3 is not a hydrogen atom, and a phenyl group and a benzyl group may optionally be substituted by a halogen atom, a C_1-C_3 alkoxy, alkyl or thioalkyl group, a nitro group, a trifluoromethyl group or a hydroxy group, and these alkyl and alkoxy groups are straight chain, branched chain or cyclic ones, respectively); n is 0, 1 or 2; p is 0 or 1; one of A, B, C and D is N, and the other ones are each CH, or all A, B, C and D are each CH.

On the other hand, there are known some acetamide derivatives having a 2-phenyl-4-pyrimidinylamino moiety. For example, USP 3631036 discloses some compounds represented by 2-(5-cyano-2-phenyl-4-pyrimidinylamino)acetamide as a synthetic intermediate for 5-amino-2,6-di-substituted-7H-pyrrolo[2,3-d]pyrimidines. USP 3631045 discloses some compounds represented by 2-(5-cyano-6-methylamino-2-phenyl-4-pyrimidinylamino)acetamide as a synthetic intermediate for 4,5-diamino-7H-pyrrolo[2,3-d]pyrimidines. However, the pharmacological activities of these compounds have never been disclosed yet.

Besides, Pharmazie, 43, 537-538 (1988) discloses some compounds represented by 2-(5-acetyl-6-methyl-2-phenyl-4-pyrimidinylthio)-N-(4-chlorophenyl)acetamide and 2-(5-acetyl-6-methyl-2-phenyl-4-pyrimidinylthio)-N-(4-methylphenyl)acetamide, as a synthetic intermediate for thieno[2,3-d]pyrimidine derivatives. Moreover, it is also disclosed in said literature that 2-(5-acetyl-6-methyl-2-phenyl-4-pyrimidinylthio)-N-(4-chlorophenyl)acetamide shows antibacterial activity against *Bacillus subtilis*.

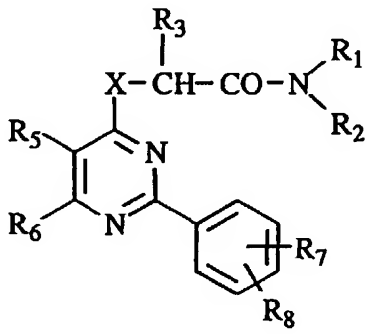
DISCLOSURE OF INVENTION

The present inventors have intensively studied in order to prepare a compound acting selectively and potently on $BZ\omega_3$-receptor, and have found the acetamide derivatives of the following formula (I), and finally have accomplished the present invention.

An object of the present invention is to provide a novel acetamide derivative acting selectively and potently on

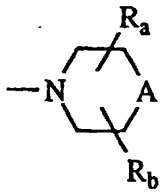
$BZ\omega_3$-receptor, more particularly, to provide an acetamide derivative having a 2-phenyl-4-pyrimidinylamino moiety or a 2-phenyl-4-pyrimidinyloxy moiety. Especially, the present invention provides a useful compound having an anxiolytic activity and being useful in the treatment of immune diseases. Another object of the present invention is to provide a process for preparing said compound. Still further object of the present invention is to provide a pharmaceutical composition containing said compound. These objects and the advantageous features of the present invention are obvious to any skilled person in this art from the following description.

The present invention provides an acetamide derivative of the following formula (I), a pharmaceutically acceptable acid addition salt thereof (hereinafter, occasionally referred to as "the compound of the present invention"), a process for preparing the same, and a pharmaceutical composition containing the same.



(I)

wherein X is —O— or —NR_4—,
R_1 is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a cyclolalkyl-lower alkyl group,
R_2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, or R_1 and R_2 may optionally combine together with the nitrogen atom to which they are attached to form a group of the formula:



wherein A is a single bond, —CH_2—, —O— or —NH—, R_a and R_b are the same or different and each a hydrogen atom or a lower alkyl group, or when A is a single bond, and R_a and R_b are located at the 2-position and the 3-position, respectively, the carbon atoms of the 2-position and the 3-position and R_a and R_b may optionally combine to form a phenyl ring,

R_3 is a hydrogen atom, a lower alkyl group or a hydroxy-lower alkyl group,
R_4 is a hydrogen atom or a lower alkyl group, or R_3 and R_4 may optionally combine together with the carbon atom and the nitrogen atom to which they are attached to form pyrrolidine, piperidine, or 2,3-dihydro-1H-indole ring,
R_5 is a hydrogen atom, a lower alkyl group, a lower alkenyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted benzyloxy-lower alkyl group, an acyloxy-lower alkyl group, a lower alkoxy-lower alkyl group, a trifluoromethyl group, a halogen atom, an amino group, a mono- or di-lower alkylamino group, an acylamino group, an amino-lower alkyl group, a nitro group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a carboxyl group, a protected carboxyl group, a carboxy-lower alkyl group or a protected carboxy-lower alkyl group,
R_6 is a hydrogen atom, a lower alkyl group, a trifluoromethyl group or a substituted or unsubstituted phenyl group, or R_5 and R_6 may optionally combine to form —$(CH_2)_n$— (n is 3, 4, 5 or 6),
R_7 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy

group, an amino group, a mono- or di-lower alkylamino group, a cyano group or a nitro group,

R_8 is a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group.

The pharmaceutically acceptable acid addition salt of the compound of the formula (I) includes a pharmaceutically acceptable acid addition salt of the compound of the formula (I) which shows basicity enough to form an acid addition salt thereof, for example, a salt with an inorganic acid such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc., or a salt with an organic acid such as maleate, fumarate, oxalate, citrate, tartrate, lactate, benzoate, methanesulfonate, etc. The compound of the formula (I) and an acid addition salt thereof may exist in the form of a hydrate and/or a solvate, and the present invention also includes these hydrates and solvates as well.

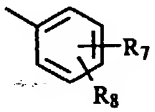
The compound of the formula (I) may have one or more asymmetric carbon atoms, and by which stereoisomers thereof are possible, and the compound of the formula (I) may exist in a mixture of two or more stereoisomers. The present invention also includes these stereoisomers, a mixture thereof, and a racemic mixture thereof.

The terms used in the present description and claims are explained below.

The lower alkyl group and the lower alkoxy group include a straight chain or branched chain alkyl or alkoxy group having 1 to 6 carbon atoms, respectively, unless defined otherwise. The lower alkyl group is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, and hexyl. The lower alkyl groups for R_3, R_4, R_5, R_6, R_7 and R_8 are preferably ones having 1 to 4 carbon atoms. The lower alkoxy group is, for example, methoxy, ethoxy, propoxy, and butoxy. The lower alkenyl group includes ones having a double bond except for between the 1- and 2-positions, and having 3 to 6 carbon atoms, for example, allyl, and 2-butenyl. The cycloalkyl group includes ones having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The cycloalkyl-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by one of the above mentioned cycloalkyl groups, for example, cyclopropylmethyl, cyclopentylmethyl, and cyclohexylmethyl. The halogen atom is fluorine, chlorine, bromine, and iodine.

The substituted or unsubstituted phenyl group includes a phenyl group which may optionally be substituted by one or two groups selected from a halogen atom, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, a trifluoromethyl group, an amino group, a mono- or di-C_1-C_3 alkylamino group, a cyano group and a nitro group, for example, phenyl; 2-, 3- or 4-chlorophenyl; 2-, 3- or 4-bromophenyl; 2-, 3- or 4-fluorophenyl; 2,4-dichlorophenyl; 2,4-dibromophenyl; 2,4-difluorophenyl; 2-, 3- or 4-methylphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl; 2-, 3- or 4-aminophenyl; 2-, 3- or 4-methylaminophenyl; 2-, 3- or 4-dimethylaminophenyl; 2-, 3- or 4-cyanophenyl; and 2-, 3- or 4-nitrophenyl.

The examples of a group of the formula:



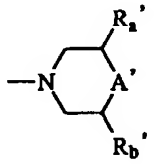
includes ones being exemplified above for the substituted or unsubstituted phenyl group, and more preferable ones are phenyl, 4- or 3-chlorophenyl, 4- or 3-bromophenyl, 4- or 3-fluorophenyl, and 4-methoxyphenyl. The substituted or unsubstituted phenyl-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by one of the above mentioned substituted or unsubstituted phenyl groups, for example, benzyl, 2-, 3- or 4-chlorobenzyl, 4-bromobenzyl, 3- or 4-fluorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, phenethyl, and 2-(4-chlorophenyl)ethyl.

The hydroxy-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by a hydroxy group, for example, hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl. The substituted or unsubstituted benzyloxy-lower alkyl group includes a lower alkyl group substituted by one or two groups selected from a benzyloxy group wherein the phenyl moiety may optionally be substituted by a halogen atom, a C_1-C_3 alkyl group and a C_1-C_3 alkoxy group, for example, benzyloxymethyl, 2-, 3- or 4-chlorobenzyloxymethyl, 3-bromobenzyloxymethyl, 4-fluorobenzyloxymethyl, 2,4- or 3,4-dichlorobenzyloxymethyl, 4-methylbenzyloxymethyl, 2-, 3- or 4-methoxybenzyloxymethyl, and 2-benzyloxyethyl. The acyl group includes an alkanoyl group having 2 to 4 carbon atom or a benzoyl group which may optionally be substituted by a halogen atom, a C_1-C_3 alkyl group or a C_1-C_3 alkoxy group, for example, acetyl, propionyl, benzoyl, 2-, 3- or 4-chlorobenzoyl, 2-, 3- or 4-bromobenzoyl, 2-, 3- or 4-fluorobenzoyl, 4-methylbenzoyl, and 4-methoxybenzoyl. The acyloxy-lower alkyl group includes a lower alkyl group substituted by an acyloxy group which is introduced from the above mentioned acyl groups, for example, acetoxymethyl, benzoyloxymethyl, 4-chlorobenzoyloxymethyl, 3-bromobenzoyloxymethyl, 4-fluorobenzoyloxymethyl, 2-methylbenzoyloxymethyl, and 4-methoxybenzoyloxymethyl. The lower alkoxy-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by an alkoxy group having 1 to 4 carbon atoms, for example, methoxymethyl, ethoxymethyl, 2-methoxyethyl, and 3-methoxypropyl.

The mono- or di-lower alkylamino group includes an amino group substituted by one or two alkyl groups having 1 to 4 carbon atoms, for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino,

and ethylmethylamino. The acylamino group includes an amino group substituted by the above mentioned acyl group, for example, acetylamino, propionylamino, benzoylamino, 4-chlorobenzoylamino, and 4-fluorobenzoylamino. The amino-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by an amino group, for example, aminomethyl, 2-aminoethyl, and 3-aminopropyl. The mono- or di-lower alkylcarbamoyl group includes a carbamoyl group substituted by one or two alkyl groups having 1 to 4 carbon atoms, for example, methylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and dipropylcarbamoyl. The protected carboxyl group includes a carboxyl group which is protected by a protecting group which can easily be removed by hydrolysis or hydrogenolysis, for example, a carboxyl group protected by a C_1-C_4 alkyl group or by a benzyl group which may optionally be substituted by one or two groups selected from a halogen atom, a C_1-C_3 alkyl group and a C_1-C_3 alkoxy group. The examples of the protected carboxyl group are methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, benzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-methylbenzyloxycarbonyl, and 4-methoxybenzyloxycarbonyl. Among them, methoxycarbonyl, ethoxycarbonyl and benzyloxycarbonyl are preferable. The protected carboxy-lower alkyl group includes an alkyl group having 1 to 4 carbon atoms which is substituted by the above mentioned protected carboxyl group, for example, methoxycarbonylmethyl, ethoxycarbonylmethyl, benzyloxycarbonylmethyl, and 2-ethoxycarbonylethyl.

Among the compounds of the present invention, the preferable one is a compound of the formula (I) wherein R_1 and R_2 are the same or different and each a lower alkyl group, or R_1 is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group, R_2 is a substituted or unsubstituted phenyl group, or R_1 and R_2 may combine together with the nitrogen atom to which they are attached to form a group of the formula:

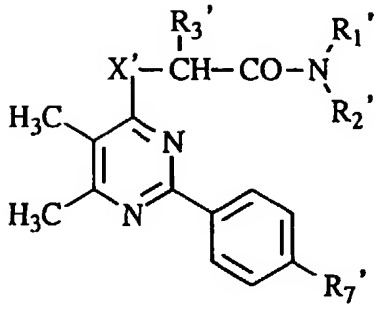


(wherein A' is $-CH_2-$ or $-O-$, R_a' and R_b' are the same or different and each a lower alkyl group), R_5 is a hydrogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a halogen atom, an amino group, an acylamino group, a nitro group or a protected carboxyl group, and X, R_3, R_6, R_7 and R_8 are the same as defined above, or a pharmaceutically acceptable acid addition salt thereof.

The more preferable compound of the present invention is a compound of the formula (I) wherein R_1 and R_2 are the same or different and each methyl group, ethyl group, propyl group, isopropyl group or butyl group, or R_1 is methyl group, ethyl group, propyl group, isopropyl group, butyl group, allyl group or cyclopropylmethyl group, R_2 is phenyl group, or a phenyl group substituted by a halogen atom or methoxy group, R_3 is a hydrogen atom, R_5 is a hydrogen atom, methyl group, ethyl group or hydroxymethyl group, R_6 is methyl group or phenyl group, or R_5 and R_6 may optionally combine to form - $-(CH_2)_4-$, R_7 is a hydrogen atom, a halogen atom, a C_1-C_3 alkoxy group, trifluoromethyl group, amino group or nitro group, R_8 is a hydrogen atom, and X and R_4 are the same as defined above, or a pharmaceutically acceptable acid addition salt thereof.

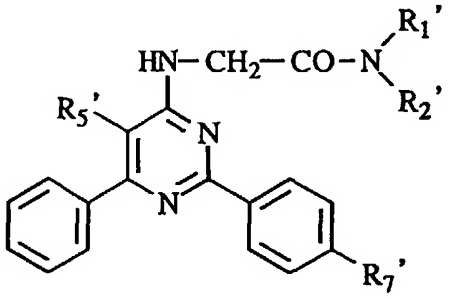
The further preferable compound of the present invention is a compound of the formula (I) wherein X is $-O-$ or $-NR_4'-$, R_1 and R_2 are the same or different and each ethyl group, propyl group or butyl group, or R_1 is methyl group, ethyl group, propyl group, allyl group or cyclopropylmethyl group, and R_2 is phenyl group, a halogenophenyl group or a methoxyphenyl group, R_3 is a hydrogen atom, R_4' is a hydrogen atom, methyl group or ethyl group, or R_3 and R_4' may optionally combine together with the carbon atom and the nitrogen atom to which they are attached to form pyrrolidine ring or 2,3-dihydro-1H-indole ring, R_7 is a hydrogen atom, a halogen atom, methoxy group, trifluoromethyl group, amino group or nitro group, R_8 is a hydrogen atom, R_5 and R_6 are the same as defined just in the above, or a pharmaceutically acceptable acid addition salt thereof.

The especially preferable compound of the present invention is an acetamide derivative of the following formula (I') or the formula (I''), or a pharmaceutically acceptable acid addition salt thereof.



(I')

wherein X' is —O— or —NR_4"—, R_1' and R_2' are both ethyl group or propyl group, or R_1' is methyl group, ethyl group, propyl group, allyl group or cyclopropylmethyl group, and R_2' is phenyl group, 4-halogenophenyl group, or 4-methoxyphenyl group, R_3' is a hydrogen atom, $R^{4"}$ is a hydrogen atom, methyl group or ethyl group, R_7' is a hydrogen atom, a halogen atom, methoxy group, a trifluoromethyl group, an amino group or a nitro group. Further, among the compounds of the formula (I'), the compounds of the formula (I") wherein X' is —O— or X' is —NH— are most preferable.



(I")

wherein R_5' is a hydrogen atom, methyl group or ethyl group, and R_1', R_2' and R_7' are the same as defined above.

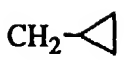
The examples of the most preferable compound of the present invention are the following compounds and pharmaceutically acceptable acid addition salts thereof.

2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-dipropylacetamide;
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-diethylacetamide;
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide;
N-(4-Chlorophenyl)-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetamide;
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-fluorophenyl)-N-methylacetamide;
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-methoxyphenyl)-N-methylacetamide;
2-(5,6-Dimethyl-2-phenyl-4-pyrimidinylamino)-N-phenyl-N-propylacetamide;
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-ethyl-N-phenylacetamide;
2-(5,6-Dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide;
2-(2,6-Diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;
2-[5,6-Dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide;
2-[2-(4-Aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide;
N-(4-Chlorophenyl)-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetamide; and
2-(5,6-Dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide

The representative compounds of the present invention are, in addition to the compounds of the following Examples, the compounds of the following Tables 1 to 4, and a pharmaceutically acceptable acid addition salt thereof.

In Tables 1 to 4, the following Reference Examples and Examples, the following abbreviations are used in order to simplify the disclosure.

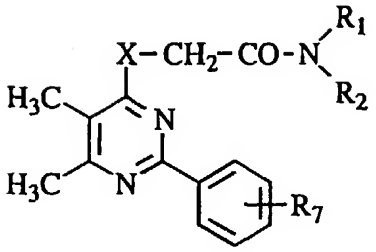
Ac: Acetyl group
Me: Methyl group
Et: Ethyl group
Pr: Propyl group
i-Pr: Isopropyl group
Bu: Butyl group
i-Bu: Isobutyl group

 : Cyclopropylmethyl group

Ph: Phenyl group

Thus, for example, Ph-4-Cl means 4-chlorophenyl group, and Ph-4-F means 4-fluorophenyl group.

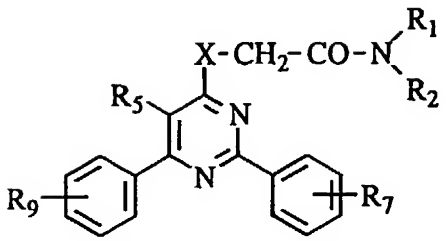
Table 1



R_1	R_2	R_7	X
Me	Ph-2-F	H	NH
Me	Ph-2-Br	H	NH
i-Pr	i-Pr	4-Cl	NH
Me	Ph-2-Cl	4-Cl	NH
Me	Ph-3-F	4-Cl	NH
Et	Ph-4-Cl	4-Cl	NH
Et	Ph-4-F	4-Cl	NH
Pr	Pr	2-Br	NH
Pr	Pr	4-Br	NH
Bu	Bu	4-Br	NH
Me	Ph	4-Br	NH
Me	Ph	4-Br	NH
Et	Ph-4-Cl	4-Br	NH
Pr	Pr	3-F	NH
Me	Ph	2-F	NH
Me	Ph-2-Cl	4-F	NH
Me	Ph-3-Cl	4-F	NH
Me	Ph-2-F	4-F	NH
Et	Ph-4-F	4-F	NH

R_1	R_2	R_7	X
Bu	Bu	4-OMe	NH
Me	Ph-3-F	4-OMe	NH
Et	Ph-4-F	4-OMe	NH
Pr	Pr	4-OH	NH
Me	Ph	4-NH_2	NH
Bu	Bu	H	NMe
Me	Ph-4-Cl	4-F	NMe
Me	Ph-4-F	4-Cl	NMe
Pr	Pr	H	NEt
Pr	Pr	4-F	NEt
Me	Ph	4-Cl	NPr
Pr	Pr	4-NH_2	O
i-Pr	i-Pr	4-Cl	O
Bu	Bu	4-Cl	O
Me	Ph	4-NH_2	O
Me	Ph-4-Cl	3-F	O
Me	Ph-2-F	4-Cl	O
Et	Ph-4-Cl	H	O
Et	Ph-4-Cl	4-F	O
Et	Ph-4-F	4-Cl	O

Table 2



R_1	R_2	R_5	R_9	R_7	X
Et	Et	H	H	4-Cl	NH
Pr	Pr	H	H	4-F	NH
Pr	Pr	H	H	2-F	NH
i-Pr	i-Pr	H	H	H	NH
Bu	Bu	H	H	H	NH
Bu	Bu	H	H	4-F	NH
Me	Ph	H	H	4-F	NH
Me	Ph	H	H	3-Cl	NH
Me	Ph-4-Cl	H	H	4-Cl	NH
Me	Ph-2-Cl	H	H	4-F	NH
Me	Ph-4-F	H	H	4-Cl	NH
Me	Ph-2-F	H	H	4-F	NH
Et	Ph	H	H	4-Cl	NH
Et	Ph-4-Cl	H	H	H	NH
Pr	Pr	Me	H	4-F	NH
i-Pr	i-Pr	Me	H	4-Cl	NH
Bu	Bu	Me	H	4-F	NH
Me	Ph	Me	H	4-Cl	NH
Me	Ph-4-Cl	Me	H	H	NH
Me	Ph-4-Cl	Me	H	4-F	NH
Me	Ph-4-F	Me	H	4-Cl	NH
Et	Ph	Me	H	H	NH
Et	Ph	Me	H	4-Cl	NH

Table 2 (continued)

R_1	R_2	R_5	R_9	R_7	X
Pr	Pr	H	4-Cl	4-F	NH
Bu	Bu	H	4-NO_2	4-F	NH
Me	Ph-4-Cl	H	2-Me	H	NH
Pr	Pr	Me	4-Cl	4-F	NH
Bu	Bu	Me	4-NO_2	4-F	NH
Me	Ph-4-Cl	Me	2-Me	H	NH
Et	Et	H	H	3-Cl	O
Pr	Pr	H	H	4-Cl	O
i-Pr	i-Pr	H	H	4-F	O
Bu	Bu	H	H	4-Cl	O
Me	Ph	H	H	4-Cl	O
Me	Ph-4-Cl	H	H	4-F	O
Et	Ph	H	H	2-Cl	O
Et	Ph-4-Cl	H	H	H	O
Et	Et	Me	H	4-Cl	O
Pr	Pr	Me	H	H	O
Pr	Pr	Me	H	4-Cl	O
i-Pr	i-Pr	Me	H	3-F	O
Bu	Bu	Me	H	2-Cl	O
Me	Ph-4-Cl	Me	H	4-F	O
Et	Ph	Me	H	4-Cl	O
Et	Ph-4-Cl	Me	H	H	O
Pr	Pr	H	4-Cl	H	O
Me	Ph-4-Cl	H	4-NO_2	4-F	O
Pr	Pr	Me	4-F	4-Cl	O
Me	Ph	Me	4-OMe	4-F	O

Table 3

R_1	R_2	n	R_7	X
Pr	Pr	3	4-Cl	NH
Pr	Pr	5	2-F	NH
Pr	Pr	3	4-F	O
Pr	Pr	5	H	O
Me	Ph	3	H	NH
Me	Ph	5	4-F	NH
Me	Ph-4-Cl	6	4-Cl	NH
Me	Ph-4-Cl	3	4-F	O
Me	Ph-4-F	5	H	O
Me	Ph-4-F	6	4-Cl	O

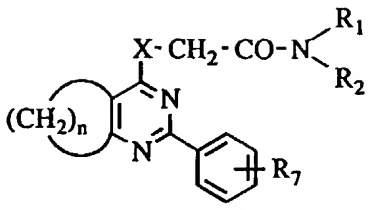
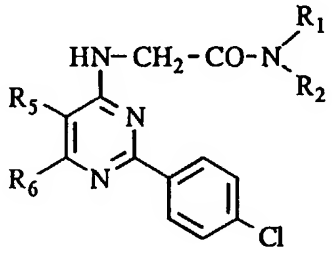


Table 4

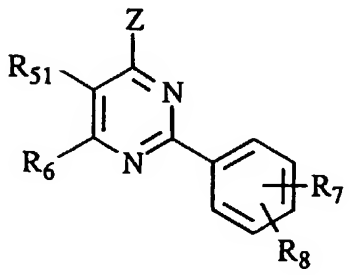
R_1	R_2	R_5	R_6	R_1	R_2	R_5	R_6
Me	Ph	$-CH_2CH_2OH$	H	Pr	Pr	Pr	Me
Pr	Pr	$-CH_2OCH_2Ph$	H	Pr	Pr	$-CH_2OH$	Me
Pr	Pr	$-CH_2OAc$	H	Pr	Pr	$-CH_2CH=CH_2$	Me
Pr	Pr	$-CH_2OCOPh$	H	Me	Ph	Me	Et
Me	Ph	$-CH_2OMe$	H	Me	Ph	Et	Et
Me	Ph	-NHMe	H	Me	Ph	Pr	Pr
Me	Ph	$-NEt_2$	H	Me	Ph	Me	CF_3
Me	Ph	$-CH_2NH_2$	H				
Me	Ph	$-CONH_2$	H				
Pr	Pr	-CONHMe	H				
Pr	Pr	$-CONEt_2$	H				
Me	Ph	-COOH	H				
Me	Ph	-COOEt	H				
Me	Ph	$-COOCH_2Ph$	H				
Pr	Pr	$-CH_2COOH$	H				
Pr	Pr	$-CH_2COOEt$	H				



The compounds of the present invention may be prepared, for example, by the following processes.

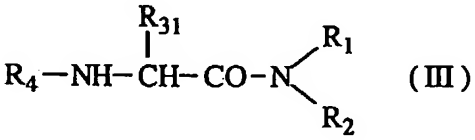
Process (a)

The compound of the formula (I) wherein X is —NR_4— is prepared by reacting a compound of the formula (II):



(II)

wherein Z is a leaving atom or a leaving group, R_{51} is the same groups as defined above for R_5 except that a hydroxy-lower alkyl group, an amino group, an amino-lower alkyl group, a carboxyl group and a carboxy-lower alkyl group are protected ones, and R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (III):



(III)

wherein R_{31} is a hydrogen atom, a lower alkyl group or a protected hydroxy-lower alkyl group, and R_1, R_2 and R_4 are the same as defined above, if necessary, followed by removing the protecting groups from the product.

The leaving atom or the leaving group represented by Z in the above formula (II) includes an atom or a group which may be removed in the form of HZ together with the hydrogen atom of the NH moiety of the compound (III) under the reaction conditions, for example, a halogen atom (e.g. chlorine, bromine, iodine), a lower alkylsulfonyloxy group (e.g. methanesulfonyloxy), a trihalogenomethanesulfonyloxy group (e.g. trifluoromethanesulfonyloxy), and an arylsulfonyloxy group (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy).

The protected hydroxy group for R_{31} or R_{51} in the above formulae (II) and (III) includes a hydroxy group being protected by a protecting group which may be removed by hydrogenolysis, for example, benzyloxy, 4-chlorobenzyloxy, 3-bromobenzyloxy, 4-fluorobenzyloxy, 4-methylbenzyloxy, and 4-methoxybenzyloxy. The protected amino group or protected amino moiety for R_{51} in the formula (II) includes an amino group or amino moiety being protected by a protecting group which can be removed by hydrogenolysis, for example, benzyloxycarbonylamino, 3- or 4-chlorobenzyloxycarbonylamino, 4-bromobenzyloxycarbonylamino, 4-fluorobenzyloxycarbonylamino, 4-methylbenzyloxycarbonylamino, and 4-methoxybenzyloxycarbonylamino. The protected carboxyl group or protected carboxyl moiety for R_{51} in the formula (II) includes a carboxyl group or carboxyl moiety being protected by a protecting group which can be removed by hydrolysis or hydrogenolysis, for example, ones which are exemplified above in the explanation of the terms used in the present disclosure and claims.

The reaction of the compound (II) and the compound (III) is carried out under atmospheric pressure or under pressure in a suitable solvent or without a solvent.

The solvent includes, for example, aromatic hydrocarbons (e.g. toluene, xylene), ketones (e.g. methyl ethyl ketone, methyl isobutyl ketone), ethers (e.g. dioxane, diglyme), alcohols (e.g. ethanol, isopropanol, butanol), acetonitrile, dimethylformamide, and dimethylsulfoxide. The reaction is preferably carried out in the presence of a base, and the base includes, for example, alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), alkali metal hydrogen carbonates (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate), and tertiary amines (e.g. triethylamine), but the excess amount of the compound (III) may be used instead of a base. The reaction temperature varies according to the kinds of the starting compounds or the reaction conditions, but it is usually in the range of about 40°C to about 200°C, more preferably in the range of about 100°C to about 170°C.

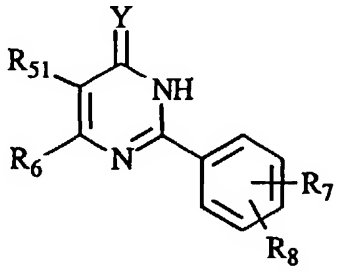
When R_{31} and/or R_{51} of the product thus obtained have a protecting group, these protecting groups may be removed by hydrogenolysis and/or hydrolysis.

The hydrogenolysis is carried out by a conventional method, for example, by reacting with hydrogen in a suitable

solvent in the presence of a catalyst such as palladium-carbon, Raney-nickel, etc. The solvent includes, for example, alcohols (e.g. ethanol, methanol), water, acetic acid, dioxane and tetrahydrofuran. The reaction is usually carried out at a temperature of from about 0°C to about 80°C, under atmospheric pressure or under pressure.

The hydrolysis is carried out by a conventional method, for example, by contacting with water in a suitable solvent under acidic or basic conditions. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol), dioxane, water, and a mixture of these solvents. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid), and organic acids (e.g. formic acid, acetic acid, propionic acid, oxalic acid). The base includes, for example, alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), and alkali metal carbonates (e.g. sodium carbonate, potassium carbonate). The reaction is usually carried out at a temperature of from about 20°C to 100°C.

The starting compound (II) is prepared by subjecting a compound of the formula (IV):



(IV)

wherein Y is an oxygen atom or a sulfur atom, and R_{51}, R_6, R_7 and R_8 are the same as defined above, to halogenation or sulfonylation by a conventional method.

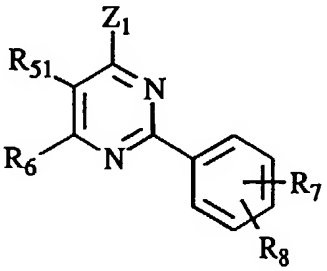
The halogenation is carried out by reacting the compound (IV) with a halogenating agent (e.g. phosphorus oxychloride, phosphorus tribromide). The sulfonylation is carried out, for example, by reacting the compound (IV) wherein Y is an oxygen atom with a sulfonylating agent (e.g. methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonyl chloride, trifluoromethanesulfonic anhydride).

The starting compound (IV) may be commercially available ones but can be prepared by a conventional method, for example, by the method disclosed in J. Am. Chem. Soc., 74, 842 (1952), Chem, Ber., 95, 937 (1962), J. Org. Chem., 29, 2887 (1964), or by the methods disclosed in the following Reference Examples 1, 20 and 41-(1), -(3), or by a modified method thereof.

Another starting compound (III) is prepared by a conventional method, for example, by the method disclosed in Japanese Patent First Publication (Kokai) No. 32058/1990, or by the methods disclosed in the following Reference Examples 45, 59 and 70, or by a modified method thereof.

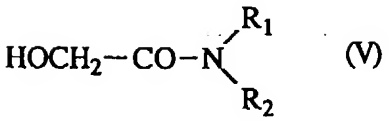
Process (b)

The compound of the formula (I) wherein X is —O— and R_3 is a hydrogen atom is prepared by reacting a compound of the formula (II'):



(II')

wherein Z_1 is a halogen atom, and R_{51}, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (V):



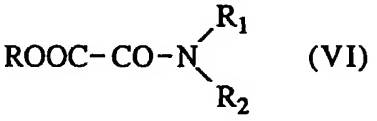
(V)

wherein R_1 and R_2 are the same as defined above, and if necessary, followed by removing the protecting groups from the product.

The reaction of the compound (II') and the compound (V) is carried out in the presence of a base in a suitable solvent or without a solvent under pressure or under atmospheric pressure. The solvent includes, for example, toluene, xylene, dimethoxyethane, 1,2-dichloroethane, acetone, methyl ethyl ketone, dioxane, diglyme, ethyl acetate, dimethylformamide and dimethylsulfoxide. The base includes, for example, sodium hydride, triethylamine, potassium carbonate, and sodium carbonate. The reaction is usually carried out at a temperature of from about —10°C to about 150°C, preferably at a temperature of from about 10°C to about 70°C.

When R_{51} in the product thus obtained has a protecting group, the protecting groups may be removed by hydrogenolysis or hydrolysis, in the same manner as in above Process (a).

The starting compound (V) is prepared by subjecting a compound of the formula (VI):



(VI)

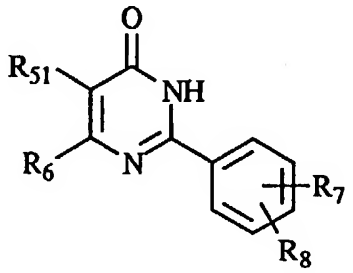
wherein R is a lower alkyl group, and R_1 and R_2 are the same as defined above, to reduction by a conventional method.

The reduction of the compound (VI) is carried out in an alcohol (e.g. methanol, ethanol), an ether (e.g. tetrahydrofuran) or a mixture of these solvents, by using a reducing agent such as lithium borohydride, at a temperature of from about —5°C to about 0°C.

The starting compound (VI) is prepared by a conventional method, or by the method disclosed in the following Reference Example 81-(1), or by a modified method thereof.

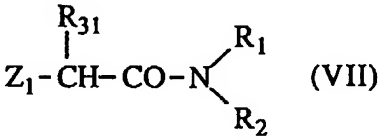
Process (c)

The compound of the formula (I) wherein X is —O— is prepared by reacting a compound of the formula (IVa):



(IVa)

wherein R_{51}, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (VII):



(VII)

wherein Z_1, R_1, R_2 and R_{31} are the same as defined above, if necessary, followed by removing the protecting groups from the product.

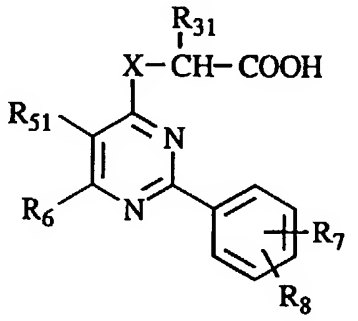
The reaction of the compound (IVa) and the compound (VII) is carried out in the same conditions such as solvent, base or reaction temperature, as those in the above Process (b).

When R_{31} and/or R_{51} of the product have a protecting group, the protecting groups may be removed by hydrogenolysis and/or hydrolysis in the same manner as in above Process (a).

The compound (VII) is prepared by a conventional method, for example, by the method disclosed in Japanese Patent First Publication (Kokai) No. 64/1987, or by the method disclosed in the following Reference Example 83, or by a modified method thereof.

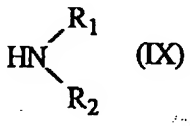
Process (d)

The compound of the formula (I) is prepared by reacting a compound of the formula (VIII):



(VIII)

wherein X, R_{31}, R_{51}, R_6, R_7 and R_8 are the same as defined above, or a reactive derivative thereof, with a compound of the formula (IX):



(IX)

wherein R_1 and R_2 are the same as defined above, if necessary, followed by removing the protecting groups from the product.

The reactive derivative of the compound (VIII) includes, for example, a lower alkyl ester (e.g. methyl ester), an active ester, an acid anhydride, and an acid halide (e.g. an acid chloride). The active ester includes, for example, p-nitrophenyl ester, 2,4,5-trichlorophenyl ester, and N-hydroxysuccinimide ester. The acid anhydride includes, for example, a symmetric acid anhydride and a mixed acid anhydride. The mixed acid anhydride includes, for example, a mixed acid anhydride with an alkyl chlorocarbonate such as ethyl chlorocarbonate, isobutyl chlorocarbonate, a mixed acid anhydride with an aralkyl chlorocarbonate such as benzyl chlorocarbonate, a mixed acid anhydride with an aryl chlorocarbonate such as phenyl chlorocarbonate, and a mixed acid anhydride with an alkanoic acid such as isovaleric acid and pivalic acid.

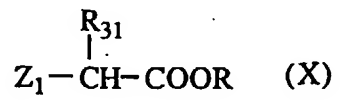
When the compound (VIII) per se is used, the reaction can be carried out in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N'-carbonyldiimidazole, N,N'-carbonyldisuccinimide, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, diphenylphosphoryl aside, propanesulfonic anhydride, and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium • hexafluorophosphate.

The reaction of the compound (VIII) or a reactive derivative thereof with the compound (IX) is carried out in a solvent or without a solvent. The solvent varies according to the kinds of the starting compounds, etc., but includes, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene), ethers (e.g. diethyl ether, tetrahydrofuran, dioxane), halogenated hydrocarbons (e.g. methylene chloride, chloroform), alcohols (e.g. ethanol, isopropanol), ethyl acetate, acetone, acetonitrile, dimethylformamide, dimethylsulfoxide, ethylene glycol, water, etc., and these solvents may be used alone, or in the form of a mixture of two or more solvents. The reaction is carried out in the presence of a base if necessary, and the base includes, for example, alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), alkali metal hydrogen carbonates (e.g. sodium

hydrogen carbonate, potassium hydrogen carbonate), and organic bases such as triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine, but the excess amount of the compound (IX) may be used instead of a base. The reaction temperature varies according to the kinds of the starting compounds, but it is usually in the range of about —30°C to about 200°C, preferably in the range of about —10°C to about 150°C.

When R_{31} and/or R_{51} of the product thus obtained have a protecting group, these protecting groups may be removed by hydrogenolysis and/or hydrolysis, in the same manner as in above Process (a).

The compound of the formula (VIII) wherein X is an oxygen atom is prepared, for example, by above Process (c), i.e. by reacting the above compound (IVa) with a compound of the formula (X):



(X)

wherein Z_1, R and R_{31} are the same as defined above, in the same manner as in Process (c), followed by subjecting the product to hydrolysis in a conventional manner.

The compound of the formula (X) is commercially available ones but can be prepared by a conventional manner.

The compound of the formula (VIII) wherein X is —NH_4— is prepared, for example, by above Process (a), i.e. by reacting the compound (II) with a compound of the formula (XI):

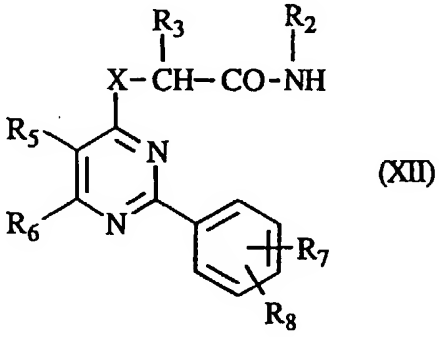
(XI)

wherein R' is a lower alkyl group, benzyl group or a benzyl group being substituted by a halogen atom, methyl group or methoxy group, and R_{31} and R_4 are the same as defined above, in the same manner as in Process (a), followed by subjecting the product to hydrolysis or hydrogenolysis in a conventional manner.

The compound (XI) is commercially available ones but can be prepared by a conventional method.

Process (e)

The compound of the formula (I) wherein R_1 is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group is prepared by reacting a compound of the formula (XII):



(XII)

wherein X, R_2, R_3, R_5, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (XIII):

$$R_{11}—Z_1 \qquad \text{(XIII)}$$

wherein R_{11} is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group, and Z_1 is the same as defined above, if necessary, followed by removing the protecting groups from the product.

The reaction of the compound (XII) and the compound (XIII) is usually carried out in a suitable solvent. The solvent

includes, for example, aromatic hydrocarbons (e.g. benzene, xylene), ketones (e.g. methyl ethyl ketone), ethers (e.g. dioxane), and dimethylformamide. The reaction is preferably carried out in the presence of a base, and the base includes ones exemplified above in Process (a), and sodium hydride. The reaction temperature varies according to the kinds of the starting compounds or the reaction conditions, but it is usually in the range of about 0°C to about 200°C, and when sodium hydride is used as a base, it is in the range of about 0°C to about 50°C.

When R_{31} and/or R_{51} of the product have a protecting group, the protecting groups may be removed by hydrogenolysis and/or hydrolysis.

The compound (XII) is prepared by using the compound (VIII) and the compound (IX) wherein R_1 is a hydrogen atom in above Process (d).

The compound (XIII) may be commercially available ones but can be prepared by a conventional method.

In above Processes (a) to (e), when the starting compounds used therein have a group which may participate in the reaction, it is convenient to protect said group with a protecting group, or to convert it previously into a group which can easily be converted into said group after the reaction. For example, a part of the compound (I) is prepared by the following processes.

The compound of the formula (I) wherein R_5 is an amino group is prepared by subjecting the compound (I) wherein R_5 is a nitro group to reduction by a conventional method. This process is explained below in Examples 122 and 124.

The compound of the formula (I) wherein R_5 is an acylamino group is prepared by reacting the compound (I) wherein R_5 is an amino group with a corresponding carboxylic acid or a reactive derivative thereof. This process is explained below in Example 125.

The compound of the formula (I) wherein R_5 is a hydroxy-lower alkyl group is prepared by subjecting the compound (I) wherein R_5 is an alkoxycarbonyl group or an alkoxycarbonyl-lower alkyl group wherein the alkyl moiety has carbon atoms fewer by one carbon atom, to reduction by a conventional method. This process is explained below in Example 127.

The compound of the formula (I) wherein R_8 is a hydroxy group is prepared by treating the compound (I) wherein R_8 is a methoxy group with hydrogen bromide.

The desired compounds obtained in the above Processes can be isolated and purified by a conventional method such as chromatography, recrystallization, re-precipitation, etc. The compound (I) which shows basicity enough to form an acid addition salt thereof is converted into an acid addition salt thereof by treating it with various acids by a conventional method.

Various stereoisomers of the compound (I) can be separated and purified by a conventional method such as chromatography, etc.

The pharmacological activities of the present compounds are explained by the following pharmacological experiments on the representative compounds of the present invention.

Experiment 1: Central (ω_1, ω_2) and peripheral (ω_3) benzodiazepine (BZ) receptor binding assays

$BZ\omega_1$ and $BZ\omega_2$ receptor binding assays were carried out according to the method of Stephens, D. N. et al. [cf. J. Pharmacol. Exp. Ther. 253, 334-343 (1990)], and $BZ\omega_3$ receptor binding assay was done according to the method of Schoemaker, H. [cf. J. Pharmacol. Exp. Ther. 225, 61-69 (1983)] each with slight modification.

Receptor membrane fractions for ω_1, ω_2 and ω_3 were prepared from the cerebellum (ω_1), spinal cord (ω_1) or kidney (ω_3) in 7-8 week old male rats of Wistar strain by the procedure described below.

After the cerebellum or spinal cord was homogenized with 20 volumes of ice-cold 50 mM Tris-citrate buffer (pH 7.1), the homogenate was centrifuged for 15 minutes at 40,000 g. The pellet obtained was washed 4 times by the same procedure, frozen and stored for 24 hours at -60°C. The resulting pellet, after being thawed, washed with the buffer and centrifuged, was suspended in the buffer I for the binding assay (50 mM Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$; pH 7.4) and the suspension thus obtained (containing 1 g wet tissue/40 ml) was used for the $BZ\omega_1$ and $BZ\omega_2$ receptor binding assays. On the other hand, the kidney was homogenized with 20 volumes of the ice-cold buffer II for the binding assay (50 mM Na-K phosphate buffer containing 100 mM NaCl; pH 7.4), filtered through 4 sheets of gauze, and centrifuged for 20 minutes at 40,000 g. The pellet obtained was suspended in the buffer II and the suspension (containing 1 g wet tissue/100 ml) was used for the binding assay as $BZ\omega_3$ receptor membrane source.

[^{3}H] Flumazenil (final concentration: 0.3 nM for ω_1 and 1 nM for ω_2) and flunitrazepam (final concentration: 10 μM) were used for the $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays as the isotope-labeled and unlabeled ligands, respectively. For the $BZ\omega_3$ receptor binding assay, [^{3}H] 4'-chlorodiazepam (7-chloro-1,3-dihydro-1-methyl-5-(4-chlorophenyl)-2H-1,4-benzodiazepin-2-one) (final concentration: 0.5 nM) and diazepam (final concentration: 100 μM) were used as the isotope-labeled and unlabeled ligands, respectively. Incubation was performed for 30 minutes at 37°C in the $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays, and for 150 minutes at 0°C in the $BZ\omega_3$ receptor binding assay. The $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays were carried out in the presence of bicuculline (final concentration: 100 μM).

The binding assay was performed by the following procedure. After adding each test compound at certain known concentrations, a [^{3}H] ligand and the buffer I or II to each test tube, each assay was started by addition of membrane preparation (total volume of 1 ml). After incubation, the assay was terminated by filtration with suction through a Whatman GF/B glass fiber filter using a cell harvester (Brandel, USA). The filters were rapidly washed 3 times with 5 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.7) for ω_1 and ω_2, or the buffer II for ω_3, and transferred to scintillation vials containing 10 ml liquid scintillation cocktail (ACS-II, Amersham, USA). After a few hours, retained radioactivity was counted by a liquid scintillation spectrometer. Specific binding of [^{3}H] ligands was calculated as the difference between amounts of radioactivity bound in the presence and absence of excess unlabeled ligands. The concentration of the test compounds causing 50% inhibition of specific binding of the [^{3}H] ligand (IC_{50}) was determined by probit analysis. The results of benzodiazepine ω_3 receptor binding assay are shown in Table 5. It is noted that all the compounds listed in Table 5 had affinity for the $BZ\omega_1$ and $BZ\omega_2$ receptors with IC_{50} values larger than 1000 nM.

Table 5

Test Comp.	ω_3 IC_{50} (nM)	Test Comp.	ω_3 IC_{50} (nM)
1*	3.10	58	1.62
2	0.97	61	9.80
4	4.36	65	1.66
5	1.28	68	2.19
6	0.23	69	2.75
10	0.70	70	1.12
15	3.86	76	1.33
16	4.00	79	0.87
17	1.97	81	6.90
22	3.26	83	5.02
23	1.76	84	2.04
25	1.93	85	0.18
26	0.28	93	4.10
27	0.11	97	2.27
29	0.85	102	3.31
35	1.51	103	2.90
36	1.44	104	3.44
37	1.66	105	4.18
41	2.53	106	4.24
42	2.15	107	4.23
44	4.98	108	1.21
45	0.70	109	2.09
47	0.16	110	1.99
49	0.23	111	2.05
51	0.32	112	2.34
52	29.5	118	1.07
57	5.39	119	1.45

*: The compound of Example 1 (hereinafter, the compounds of Examples in the same way)

Test Comp.	ω_3 IC_{50} (nM)	Test Comp.	ω_3 IC_{50} (nM)
120	1.63	160	4.30
124	5.35	161	1.05
127	4.35	162	1.19
128	0.79	163	2.64
130	1.31	164	0.29
131	0.89	165	5.07
133	2.20	166	5.40
134	3.07	167	0.79
135	3.17	168	0.99
136	0.34	169	1.15
137	0.93	170	0.99
138	0.53	171	1.56
139	0.38	175	1.90
141	0.11	178	0.57
142	0.08	179	4.30
143	1.40	180	1.65
144	0.31	181	1.61
145	1.60	182	4.57
147	0.52	183	8.75
149	1.14	184	0.82
151	0.58	186	2.39
155	0.76	187	9.71
156	4.96	188	5.24
158	4.07	190	4.00
159	2.00	195	2.00

The compounds listed in Table 5 bind strongly to the $BZ\omega_3$ receptor, but have affinity for the $BZ\omega_1$ and B ω_2 receptors with the IC_{50} value larger than 1000 nM. Therefore, it is evident that the compounds of the present invention have potent and highly selective affinity for the $BZ\omega_3$ receptor.

Experiment 2: Light and dark box test (anti-anxiety effect)

Anti-anxiety effect of test compounds was examined in a box with light and dark compartments according to the method of Crawley, J. and Goodwin, F.K. [cf. Pharmacol. Biochem. Behav. 13, 167-170 (1980)] with slight modification.

Light and dark box test is a useful, simple and handy method for behaviorally and pharmacologically examining anti-anxiety effect of the drugs, by utilizing the habit of rodents such as mice and rats, etc. which prefer to stay in a dark place, and regarding as positive drug effect the increase of the relative stay of the animals in the light compartment

which is an uncomfortable place for the animals. A number of drugs such as cholecystokinin B type receptor antagonists and BZ anxiolytics, etc. show positive effect in this test.

Light and dark box test was carried out using the test box device (35 X 15 X 17 cm) which comprises: a light compartment (20 X 15 X 17 cm) consisting of transparent acrylic plates and highly illuminated by an incandescent lamp (1,700 lux); a dark compartment (15 X 15 X 17 cm) being made of black acrylic plates connected to the light compartment; and at the boundary of compartments, an opening (4.4 X 5 cm) in which mice can go through freely between two compartments.

Male mice of Std-ddY strain weighing 25-30 g were used in a group of 10. Each trial was started by placing a mouse in the center of the light compartment 30 minutes after oral administration of a test compound, and the time spent by the mouse in the light compartment during a 5 minute observation period was measured, and the rate of the stay of mice in the light compartment to the whole time spent in the experiment was calculated. The increasing rate of the relative stay of the test compound to that of the vehicle control group was yielded, based on the rate of the stay of mice in the light compartment.

The anti-anxiety effect of the test compound was represented by the minimum effective dose (MED) at which the increasing rate of the relative stay was regarded statistically as significant (Williams-Wilcoxon's test, $p<0.05$). The results are shown in Table 6.

Table 6

Test Comp.	Anti-anxiety effect	Test Comp.	Anti-anxiety effect
	MED (mg/kg)		MED (mg/kg)
1*	0.3	31	0.3
2	0.01	35	0.1
6	0.3	36	0.3
9	0.3	37	0.1
10	1.0	42	< 0.01
16	0.1	45	0.1
21	0.1	52	0.1
22	0.3	136	0.3
23	0.01	139	0.1
29	0.03	150	0.3

*: The compound of Example 1 (hereinafter, the compounds of Examples in the same way)

Test compounds in Table 6 have anti-anxiety effect at doses of 1 mg/kg or below. Among them, many compounds are effective at doses of 0.3 mg/kg or below.

Experiment 3: Isoniazid-induced clonic convulsion test (anti-convulsant effect)

Isoniazid inhibits glutamate decarboxylase which catalyzes GABA synthesis, decreases brain GABA levels, and induces clonic convulsion. According to the method of Auta, J. et al. [cf. J. Pharmacol. Exp. Ther. 265, 649-656 (1993)] with slight modification, we examined antagonistic effect of the test compounds on isoniazid-induced clonic convulsion. Many drugs which, directly or indirectly, enhance $GABA_A$ receptor function are known to exhibit positive effect in this test. Those are BZ anxiolytics represented by diazepam, neurosteroids such as allopregnanolone, allotetrahydrodeoxycorticosterone(THDOC) and $BZ\omega_3$ receptor agonists which enhance the synthesis of neurosteroids.

Male mice of Std-ddY strain weighing 22-24 g were used in a group of 6. Thirty minutes after oral administration of the test compounds, mice were injected with isoniazid (200 mg/kg, s.c.), and immediately thereafter, placed individually in acrylic observation cages. The onset time of clonic convulsion was measured (cut-off time: 90 minutes). The latency in the control group was about 40 minutes.

Anti-isoniazid effect of the test compounds was expressed as the dose which prolonged the onset time by 25% compared to that in the vehicle group (ED_{25}). The ED_{25} value was calculated according to the Litchfield-Wilcoxon's method. The results are shown in Table 7.

Table 7

Test Comp.	Anti-isoniazid effect	Test Comp.	Anti-isoniazid effect
	ED_{25} (mg/kg)		ED_{25} (mg/kg)
1*	82.2	44	22.4
2	65.6	45	9.60
4	51.2	47	7.62
5	15.1	48	7.67
9	25.5	50	27.3
10	36.9	52	23.5
11	47.5	53	11.3
12	31.8	58	11.8
17	45.7	59	14.8
21	72.1	60	2.14
22	50.3	61	17.7
23	40.8	65	31.1
25	62.1	66a	51.2
29	67.5	66b	72.4
35	85.7	79	43.8
36	54.2	83	70.2
37	61.9	171	76.4
42	58.7		

*: The compound of Example 1 (hereinafter, the compounds of Examples in the same way)

The test compounds in Table 7 exhibited anti-convulsant effect at doses lower than 100 mg/kg. Some of them caused the effect at doses below 10 mg/kg.

Experiment 4: Collagen-induced arthritis inhibitory test 1

Collagen-induced arthritis inhibitory test is an experimental model for rheumatoid arthritis reported by Trethan, D. E. et al. [cf. J. Exp. Med., 146, 857 (1977)], and thereafter Kakimoto, K. et al. demonstrated that collagen-induced arthritis inhibitory test was useful as an evaluating tool for not only anti-inflammatory agents, but also immuno suppressing agents and immuno modulating agents, based on the mechanism of onset of the disease [cf. J. Immunol., 140, 78-83 (1988)].

Collagen-induced arthritis inhibitory test was carried out according to Kakimoto, K. et al. (cf. above reference of Kakimoto, K. et al.) with slight modification. Solubilized bovine cartilage type II collagen (product of Elastine Products, U.S.A.) was emulsified in complete Freund's adjuvant (product of DIFCO Lab., U.S.A.). Male mice of DBA/1j strain (6 week-old; product of Nippon Charles River, Japan) were immunized by injection at the base of the tail with 150 μg of the emulsified collagen. After twenty one days from the immunization, arthritis was induced by a booster immunization of 150 μg of the emulsified collagen prepared in the same manner as above at the base of the tail again. A test compound was orally administered daily at the dose of 10 mg/kg from the first immunization. Mice were observed daily 5 days after the booster immunization for the onset of arthritis, and an arthritic score was derived by grading the severity of involvement of each paw five scales (0-4) according to the method of Wood, F. D. et al. [cf. Int. Arch. Allergy Appl. Immunol., 35, 456-467 (1969)] with slight modification as shown in Table 8. The severity of arthritis was estimated by the sum of the scores of all 4 paws, and the onset of the disease was determined when score 1 was observed.

Table 8

Score	Symptoms
0	No changes
1	Erythema and swelling of one interphalangeal joint of the fingers of 4 paws
2	Erythema and swelling of two or more interphalangeal joints, or relatively large joints of wrist, ankle, etc.
3	Gross swelling and erythema
4	Reaching the maximum level of swelling of the entire paw

In the mice which were administered with the compound of Example 93, the onset of arthritis was delayed until 40 days, after the booster immunization, while in the control mice which were injected with the solvent, the onset of arthritis was observed on 28th day. In the mice which were administered with the compound of Example 136 and Example 144, the onset of arthritis was delayed until 34 days and 37 days, respectively, after the booster immunization. The severity of arthritis in the compound-treated group (Example 93, 136 and 144) was much lower than the control group in the severity of the disease judging from the score of arthritis.

Experiment 5: Collagen-induced arthritis inhibitory test 2

Collagen-induced arthritis inhibitory test was carried out according to Kakimoto, K. et al. (cf. above reference of Kakimoto, K. et al.) with slight modification. Type II collagen from bovine joints (product of the Collagen Research Center, Japan) was emulsified in complete Freund's adjuvant (product of DIFCO Lab., U.S.A.). Female mice of DBA/1j strain (product of Nippon Charles River, Japan) were immunized by injection at the base of the tail with 150 μg of the emulsified collagen. After twenty one days from the immunization, arthritis was induced by a booster immunization of 150 μg of the emulsified collagen prepared in the same manner as above at the base of the tail again. Test compounds were administered orally at a dose of 10 mg/kg on 5 consecutive days in a week for 8 weeks, beginning from the day before the immunization. Mice were monitored visually for arthritis once a week beginning from the day of the booster immunization. Each paw was individually scored on a scale of 0-3, according to the criteria shown in Table 9. The severity of arthritis was estimated by the sum of the scores of all 4 paws.

Table 9

Score	Symptoms
0	No changes
1	Erythema and swelling of one or more interphalangeal joints of the paw
2	Erythema and swelling of two or more large joints which extends to the back of the paw in addition to Erythema and swelling of one or more interphalangeal joints of the paw
3	Severe erythema and swelling of the entire paw

In the mice which were administered with the compound of Example 6, the onset of arthritis was delayed until 21 days after the booster immunization as compared with the control mice which were injected with the solvent, and the severity of arthritis in the compound-treated group was much lower than the control group at least until day 34, the last day of the experiment. The compound of Example 165 markedly suppressed the arthritis as compared with control group, at least until 34th day, the last day of the experiment. In the mice which were administered with the compound of Example 178, the arthritis was suppressed as compared with the control.

From the results clearly shown in the above experiments 4 and 5, the compounds of Examples 6, 93, 136, 144 and 165 exhibit potent effect on collagen-induced arthritis inhibitory test which is a model for immuno inflammatory diseases (rheumatoid arthritis, etc.). The compound of Example 178 has also effect, but less potent effect as compared with that of each compound as indicated above.

Experiment 6: Acute toxicity

Male mice of Std-ddY strain weighing 24-31 g were used in a group of 10 for examining acute toxicity of test com-

pounds (Example 2, 10, 23, 36, 42 and 52). A compound (1000 mg/kg) was suspended in 0.5% tragacanth and administered orally or intraperitoneally. Then, lethality of the mice was observed for 7 days after the treatment.

No lethality was found in mice to which the test compound was administered.

The compound of formula (I) and its pharmaceutically acceptable salts not only bind to the $BZ\omega_3$ receptor selectively and strongly, but also produce excellent pharmacological effects such as anti-anxiety effect and anti-convulsant effect, etc. in animal experiment, therefore, are useful for the therapy or prevention of CNS diseases [anxiety-related diseases (neurosis, somatoform disorders, other anxiety disorders), depression, epilepsy, etc.] and cardiovascular diseases (cardiac angina, hypertension, etc.).

There are listed, for example, the following compounds and pharmaceutically acceptable salts thereof which show not only selective and strong affinity for $BZ\omega_3$ receptor, but also strong anti-anxiety effect.

(1) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-dipropylacetamide (the compound of Example 2)
(2) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide (the compound of Example 23)
(3) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-diethylacetamide (the compound of Example 10)
(4) N-(4-Chlorophenyl)-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetamide (the compound of Example 29)
(5) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-fluorophenyl)-N-methylacetamide (the compound of Example 36)
(6) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-methoxyphenyl)-N-methylacetamide (the compound of Example 42)
(7) 2-(5,6-Dimethyl-2-phenyl-4-pyrimidinylamino)-N-phenyl-N-propylacetamide (the compound of Example 52)
(8) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-ethyl-N-phenylacetamide (the compound of Example 45)

The compounds of formula (I) have inhibitory effect on collagen-induced arthritis, therefore, are useful for the therapy or prevention of immune diseases such as immuno inflammatory diseases (rheumatoid arthritis, etc.) and immunoneurologic diseases (multiple sclerosis, etc.).

There are listed, for example, the following compounds and pharmaceutically acceptable salts thereof which show inhibitory effect on collagen-induced arthritis.

(1) 2-(5,6-Dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide (the compound of Example 136)
(2) 2-(2,6-Diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide (the compound of Example 93)
(3) 2-[5,6-Dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide (the compound of Example 6)
(4) 2-[2-(4-Aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide (the compound of Example 165)
(5) 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-methyl-N-phenylacetamide (the compound of Example 144)
(6) 2-(5,6-Dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide (the compound of Example 178)

The compounds [I] of the present invention or a pharmaceutically acceptable acid addition salt thereof can be administered either orally, parenterally or rectally. The dose of the compounds of the present invention varies according to the kinds of the compound, the administration routes, the conditions, ages of the patients, etc., but it is usually in the range of 0.01-50 mg/kg/day, preferably in the range of 0.03-5 mg/kg/day.

The compounds of the present invention is usually administered in the form of a pharmaceutical preparation which is prepared by mixing thereof with a pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent may be any conventional ones which are usually used in the pharmaceutical field, and do not react with the compounds of the present invention. Suitable examples of the pharmaceutically acceptable carrier or diluent are, for example, lactose, inositol, glucose, mannitol, dextran, cyclodextrin, sorbitol, starch, partly pregelatinized starch, white sugar, magnesium metasilicate aluminate, synthetic aluminum silicate, crystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl starch, calcium carboxylmethylcellulose, ion exchange resin, methylcellulose, gelatin, gum arabic, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, alginic acid, sodium alginate, light anhydrous silicic acid, magnesium stearate, talc, carboxyvinyl polymer, titanium oxide, sorbitan fatty acid ester, sodium laurylsulfate, glycerin, glycerin fatty acid ester, purified lanolin, glycerogelatin, polysorbate, macrogol, vegetable oil, wax, propyleneglycol, water, ethanol, polyoxyethylene-hydrogenated caster oil (HCO), sodium chloride, sodium hydroxide, hydrochloric acid, disodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, glutamic acid, benzyl alcohol, methyl p-oxybenzoate, ethyl p-oxy-

benzoate, etc.

The pharmaceutical preparation is, for example, tablets, capsules, granules, powders, syrups, suspensions, suppositories, injection preparations, etc. These preparations may be prepared by a conventional method. In the preparation of liquids, the compound of the present invention may be dissolved or suspended in water or a suitable other solvent, when administered. Tablets and granules may be coated by a conventional method. In the injection preparations, it is preferable to dissolve the compound of the present invention in water, but if necessary, it may be dissolved by using an isotonic agent or a solubilizer, and further, a pH adjustor, a buffering agent or a preservative may be added thereto.

These preparations may contain the compound of the present invention at a ratio of at least 0.01 %, preferably at a ratio of 0.1-70 %. These preparations may also contain other therapeutically effective compounds as well.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by the following Reference Examples and Examples, but should not be construed to be limited thereto.

The identification of the compounds is carried out by Elementary analysis, Mass spectrum, IR spectrum, NMR spectrum, etc.

The following abbreviations may be used in the following Reference Examples and Examples in order to simplify the disclosure.

[Solvent for recrystallization]

A: Ethanol
AC: Acetonitrile
E: Diethyl ether
EA: Ethyl acetate
HX: n-Hexane
IP: Isopropanol
M: Methanol

Reference Example 1

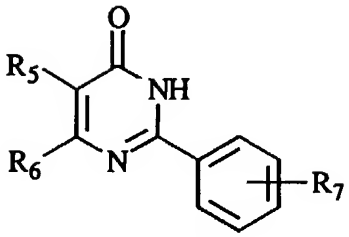
Preparation of 5,6-dimethyl-2-phenyl-4(3H)-pyrimidinone:

To a mixture of sodium ethoxide (31.3 g) and anhydrous ethanol (200 ml) is added benzamidine hydrochloride (23.9 g) at 0-5°C. The mixture is stirred at 0°C for 30 minutes, and thereto is added dropwise a solution of ethyl 2-methylacetoacetate (20 g) and anhydrous ethanol (50 ml) at the same temperature. After addition, the mixture is stirred at room temperature for 30 minutes, and refluxed for six hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in water. The pH value of the mixture is adjusted to pH 4 by addition of conc. hydrochloric acid while the mixture is stirred at 0-5°C. The precipitates are collected by filtration, washed with water, further washed with diethyl ether, and recrystallized from ethanol to give the desired compound (14.3 g), m.p. 205-207°C.

Reference Examples 2-19

The corresponding starting compounds are treated in the same manner as in Reference Example 1 to give the compounds as listed in Table 10.

Table 10



Ref. Ex.	R_5	R_6	R_7	M.p. (°C)	Solv. for recrystal.
2	Me	Me	4-Cl	258-260	M
3	Me	Me	3-Cl	251-252	A
4	Me	Me	4-F	266-268	M
5	Me	Me	4-OMe	233-235	M
6	Me	Me	4-CF_3	265-267	M
7	Me	Me	4-NO_2	>300	M
8	Me	Et	H	195-197	M
9	Me	i-Pr	H	230-232	M
10	Et	Me	H	159-161	A
11	H	Me	H	212-214	A
12	H	CF_3	H	228-230	A
13	H	Ph	H	281-284	A
14	H	Ph	4-Cl	>300	M
15	Me	Ph	H	250-252	M
16	Me	Ph	4-Cl	293-295	M
17	-$(CH_2)_4$-		H	223-225	A
18	-$(CH_2)_4$-		4-Cl	290-292	M
19	COOEt	H	H	237-238	A

Reference Example 20

Preparation of 5-nitro-2-phenyl-4(3H)-pyrimidinone:

To a mixture of sodium methoxide (8 g) and anhydrous ethanol (100 ml) is added benzamidine hydrochloride (11.7 g) at 0°C. The mixture is stirred at 0°C for 30 minutes, and thereto is added dropwise a solution of crude ethyl 2-(N,N-dimethylaminomethylene)nitroacetate (14 g), which is obtained by refluxing a mixture of ethyl nitroacetate (10 g) and N,N-dimethylformamide dimethyl acetal (10.7 g) for three hours, followed by concentrating the mixture under reduced pressure, in anhydrous ethanol (50 ml) at the same temperature. After addition, the mixture is stirred at room temperature for 30 minutes, and refluxed for 12 hours. The reaction mixture is concentrated under reduced pressure, and water

(150 ml) is added to the residue. The pH value of the mixture is adjusted to pH 4 by addition of conc. hydrochloric acid while the mixture is stirred at 0°C. The precipitates are collected by filtration, washed with water, and recrystallized from ethanol to give the desired compound (7 g), m.p. 264-266°C.

Reference Example 21

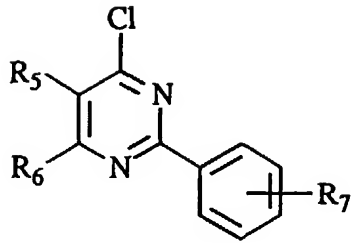
Preparation of 4-chloro-5,6-dimethyl-2-phenylpyrimidine:

A mixture of 5,6-dimethyl-2-phenyl-4(3H)-pyrimidine (10 g) and phosphorus oxychloride (23 g) is stirred at 75°C for four hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in chloroform. To the mixture is added ice-water, and the mixture is stirred. The mixture is neutralized with 1N aqueous sodium hydroxide solution, and the chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from ethanol to give the desired compound (10.7 g), m.p. 120-122°C.

Reference Examples 22-40

The corresponding starting compounds are treated in the same manner as in Reference Example 21 to give the compounds as listed in Table 11.

Table 11



Ref. Ex.	R_5	R_6	R_7	M.p. (°C)	Solv. for Recrystal.
22	Me	Me	4-Cl	122-124	IP
23	Me	Me	3-Cl	96-97	A
24	Me	Me	4-F	138-139	IP
25	Me	Me	4-OMe	106-108	IP
26	Me	Me	4-CF_3	70-71	IP
27	Me	Me	4-NO_2	157-158	A
28	Me	Et	H	87-88	IP
29	Me	i-Pr	H	83-84	IP
30	Et	Me	H	57-58	IP
31	H	Me	H	62-63	IP
32	H	CF_3	H	45-46	IP
33	H	Ph	H	99-100	IP
34	H	Ph	4-Cl	125-126	IP
35	Me	Ph	H	116-117	IP
36	Me	Ph	4-Cl	126-128	IP
37	-$(CH_2)_4$-		H	100-101	IP
38	-$(CH_2)_4$-		4-Cl	114-115	IP
39	NO_2	H	H	160-161	A
40	COOEt	H	H	39-40	HX

Reference Example 41

Preparation of 4-chloro-2-(4-fluorophenyl)-5,6,7,8-tetrahydroquinozoline:

(1) A mixture o 4-fluorobenzoyl chloride (50 g), potassium thiocyanate (36.7 g) and anhydrous toluene (100 ml) is refluxed for six hours. After cooling, the reaction mixture is filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by distillation under reduced pressure to give 4-fluorobenzoyl isothiocyanate (55 g), b.p. 92°C/3 mmHg.

(2) To a mixture of the above product (62 g) and chloroform (80 ml) is added dropwise a solution of 1-morpholino-cyclohexene (28.6 g) and chloroform (30 ml) with stirring while the temperature of the mixture is kept at 0-5°C. After addition, the reaction mixture is stirred at 0°C for one hour, and further stirred at room temperature for one hour,

and refluxed for one hour. The reaction mixture is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give 2-(4-fluorophenyl)-5,6,7,8-tetrahydro-4H-1,3-benzoxazine-4-thione (24 g), m.p. 148-149°C.

(3) Into a mixture of the above product (20 g) and methanol (300 ml) is blown ammonia gas for 30 minutes, and the mixture is stirred at 80°C for 30 minutes. The reaction mixture is concentrated under reduced pressure, and the residue is recrystallized from ethanol to give 2-(4-fluorophenyl)-5,6,7,8-tetrahydro-4(3H)-quinazolinethione (18 g), m.p. 198-200°C.

(4) A mixture of the above product (10 g) and phosphorus oxychloride (30 g) is refluxed for two hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in chloroform. To the mixture is added ice-water, and the mixture is stirred. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from isopropanol to give the desired compound (8.5 g), m.p. 96-97°C.

Reference Examples 42-44

The same procedures as Reference Example 41 are repeated except that the corresponding starting compounds are used instead of 4-fluorobenzoyl chloride to give the following compounds.

(Reference Example 42)

4-Chloro-2-(2-chlorophenyl)-5,6,7,8-tetrahydroquinazoline; m.p. 79-80°C

(Reference Example 43)

4-Chloro-2-(3-chlorophenyl)-5,6,7,8-tetrahydroquinazoline; m.p. 94-95°C

(Reference Example 44)

4-Chloro-2-(2,4-difluorophenyl)-5,6,7,8-tetrahydroquinazoline; m.p. 57-58°C

Reference Example 45

Preparation of 2-amino-N,N-dipropylacetamide:

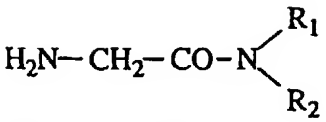
(1) To a mixture of dipropylamine (5 g), triethylamine (5 g) and methylene chloride (50 ml) is added dropwise a solution of N-phthaloylglycyl chloride (11 g) in methylene chloride (50 ml) while the temperature of the mixture is kept at 0-5°C. After addition, the mixture is stirred at room temperature for six hours. To the reaction mixture is added water, and the methylene chloride layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from isopropanol to give 2-phthalimide-N,N-dipropylacetamide (12.5 g), m.p. 99-100°C.

(2) A mixture of the above product (12.5 g), hydrazine • monohydrate (4.3 g) and ethanol (150 ml) is refluxed for one hour. The reaction mixture is concentrated under reduced pressure, and chloroform is added to the residue. The mixture is filtered, and to the filtrate is added water. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the desired compound (6.7 g) as an oily product.

Reference Examples 46-58

The corresponding starting amine compounds are treated in the same manner as in Reference Example 45 to give the compounds as listed in Table 12.

Table 12



Ref. Ex.	R_1	R_2
46	Me	Me
47	Et	Et
48	i-Pr	i-Pr
49	Bu	Bu
50	Me	i-Bu
51	Et	Pr
52	H	Ph
53	Me	Ph
54	Et	Ph
55	Bu	Ph
56	Pr	Ph
57	Me	Ph-4-Cl
58	Me	Ph-4-OMe

Reference Example 59

Preparation of 2-amino-N-(4-fluorophenyl)-N-methylacetamide:

(1) The same procedures as Reference Example 45-(1) are repeated except that 4-fluoroaniline (15 g) is used instead of dipropylamine. The product thus obtained is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give N-(4-fluorophenyl)-2-phthalimidacetamide (19 g), m.p. 212-214°C.
(2) The above product (18 g) is added to a mixture of sodium hydride (about 60 % oily, 3 g) and dimethylformamide (100 ml) at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added dropwise methyl iodide (10 g) at the same temperature. After addition, the mixture is stirred at room temperature for 8 hours. To the reaction mixture are added water and chloroform, and the chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give N-(4-fluorophenyl)-N-methyl-2-phthalimidacetamide (15 g), m.p. 182-183°C.
(3) The above product (14 g) is treated in the same manner as in Reference Example 45-(2) to give the desired compound (9.0 g) as an oily product.

Reference Example 60

Preparation of N-allyl-2-amino-N-phenylacetamide:

The same procedures as Reference Example 59 are repeated except that aniline and allyl bromide are used instead of 4-fluoroaniline in Reference Example 59-(1) and methyl iodide in Reference Example 59-(2), respectively, to give the desired compound as an oily product.

Reference Example 61

Preparation of 2-amino-N-cyclopropylmethyl-N-phenylacetamide:

The same procedures as Reference Example 59 are repeated except that aniline and cyclopropylmethyl bromide are used instead of 4-fluoroaniline in Reference Example 59-(1) and methyl iodide in Reference Example 59-(2), respectively, to give the desired compound as an oily product.

Reference Examples 62-66

The corresponding starting compounds are treated in the same manner as in Reference Example 59 to give the following compounds.

(Reference Example 62)

2-Amino-N-(4-bromophenyl)-N-methylacetamide

(Reference Example 63)

2-Amino-N-(2-chlorophenyl)-N-methylacetamide

(Reference Example 64)

2-Amino-N-(3-chlorophenyl)-N-methylacetamide

(Reference Example 65)

2-Amino-N-(4-chlorophenyl)-N-ethylacetamide

(Reference Example 66)

2-Amino-N-(4-chlorophenyl)-N-propylacetamide

Reference Examples 67-69

The corresponding starting amine compounds are treated in the same manner as in Reference Example 45 to give the following compounds.

(Reference Example 67)

1-Aminoacetyl-3,5-dimethylpiperidine

(Reference Example 68)

4-Aminoacetyl-2,6-dimethylmorpholine

(Reference Example 69)

1-Aminoacetyl-cis-3,5-dimethylpiperazine

Reference Example 70

Preparation of N-(4-chlorophenyl)-N-methyl-2-methylaminoacetamide:

(1) To a mixture of N-(tert-butoxycarbonyl)-N-methylglycine (10 g), 4-chloroaniline (8.8 g), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium • hexafluorophosphate (BOP reagent, 25.7 g) and methylene chloride (150 ml) is added dropwise triethylamine (5.9 g) while the temperature of the mixture is kept at 0-5°C. After addition, the mixture is stirred at room temperature for 8 hours, and thereto is added water. The methylene chloride layer is col-

lected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from diethyl ether to give 2-[N'-(tert-butoxycarbonyl)-N'-methylamino]-N-(4-chlorophenyl)acetamide, m.p. 126-128°C.

(2) The above product (12 g) is added to a mixture of sodium hydride (about 60 % oily, 3.2 g) and dimethylformamide (100 ml) at 0-5°C, and the mixture is stirred at 0°C for one hour, and then thereto is added methyl iodide (17 g) at the same temperature. After addition, the mixture is stirred at room temperature for 8 hours, and thereto are added water and chloroform. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform) to give 2-[N'-(tert-butoxycarbonyl)-N'-methylamino]-N-(4-chlorophenyl)-N-methylacetamide (11.4 g) as an oily product.

(3) To a mixture of the above product (8.4 g) and methylene chloride (100 ml) is added dropwise trifluoroacetic acid (20 ml) at 0-5°C. After addition, the mixture is stirred at room temperature for three hours. The reaction mixture is concentrated under reduced pressure, and to the residue is added water. The mixture is made weak basic with 1N aqueous sodium hydroxide solution while the mixture is stirred under ice-cooling, and then thereto is added chloroform. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the desired compound (4.7 g) as an oily product.

Reference Examples 71-73

The corresponding starting tert-butoxycarbonylated amino acids are treated in the same manner as in Reference Example 70 to give the following compounds as an oily product.

(Reference Example 71)

N-(4-Chlorophenyl)-N-methyl-2-pyrrolidinecarboxyamide

(Reference Example 72)

N-(4-Chlorophenyl)-N-methyl-2-piperidinecarboxyamide

(Reference Example 73)

N-(4-Chlorophenyl)-2,3-dihydro-N-methyl-1H-indole-2-carboxyamide

Reference Examples 74-80

The corresponding starting tert-butoxycarbonylated amino acids are treated in the same manner as in Reference Example 70-(1), -(3) to give the following compounds as an oily product.

(Reference Example 74)

2-Amino-3-benzyloxy-N,N-dipropylpropanamide

(Reference Example 75)

2-Methylamino-N,N-dipropylacetamide

(Reference Example 76)

2-Ethylamino-N,N-dipropylacetamide

(Reference Example 77)

2-Methylamino-N-methyl-N-phenylacetamide

(Reference Example 78)

2-Ethylamino-N-methyl-N-phenylacetamide

(Reference Example 79)

N,N-Dipropyl-2-pyrrolidinecarboxamide

(Reference Example 80)

2,3-Dihydro-N,N-dipropyl-1H-indolecarboxamide

Reference Example 81

Preparation of 2-hydroxy-N,N-dipropylacetamide:

(1) To a mixture of dipropylamine (5.0 g), triethylamine (5.5 g) and methylene chloride (70 ml) is added dropwise a solution of ethyloxalyl chloride (7.4 g) and methylene chloride (30 ml) with stirring while the temperature of the mixture is kept at —20°C. After addition, the mixture is stirred at 0°C for four hours. To the reaction mixture is added water, and the methylene chloride layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give ethyl 2-oxo-2-(N,N-dipropylamino)acetate (9.5 g) as an oily product.
(2) A mixture of the above product, sodium borohydride, lithium chloride and anhydrous tetrahydrofuran is stirred at room temperature for 30 minutes, and thereto is added dropwise anhydrous ethanol while the temperature of the mixture is kept at 0-5°C. After addition, the mixture is stirred at room temperature for 12 hours. The reaction mixture is cooled to 0°C, an the pH value thereof is adjusted to pH 5 with 1N hydrochloric acid, and concentrated under reduced pressure. To the residue are added a saturated brine and chloroform, and the chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the desired compound (7.7 g) as an oily product.

Reference Example 82

Preparation of N,N-dibutyl-2-hydroxyacetamide:

The same procedures as Reference Example 81 are repeated except that dibutylamine is used instead of dipropylamine to give the desired compound as an oily product.

Reference Example 83

Preparation of 2-bromo-N,N-dipropylacetamide:

To a mixture of dipropylamine (10.1 g), triethylamine (10.1 g) and anhydrous diethyl ether (80 ml) is added dropwise a solution of bromoacetyl chloride (15.8 g) in anhydrous diethyl ether (40 ml) while the temperature of the mixture is kept at —40°C. After addition, the temperature is gradually raised, and the mixture is stirred at room temperature for one hour. The reaction mixture is filtered, and the filtrate is concentrated under reduced pressure, and purified by distillation under reduced pressure to give the desired compound (14 g), b.p. 100-103°C/1 mmHg.

Reference Examples 84-87

The corresponding starting compounds are treated in the same manner as in Reference Example 83 to give the following compounds.

(Reference Example 84)

2-Bromo-N,N-dipropylpropanamide; b.p. 85-87°C/1 mmHg

(Reference Example 85)

2-Bromo-N-(4-chlorophenyl)-N-methylacetamide; m.p. 52-53°C
(recrystallized from isopropanol)

(Reference Example 86)

2-Bromo-N-methyl-N-phenylpropanamide; b.p. 135-145°C/1 mmHg

(Reference Example 87)

2-Bromo-N-ethyl-N-phenylpropanamide; oily product

Reference Example 88

Preparation of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetic acid:

(1) To a mixture of sodium hydride (about 60 % oily, 1.0 g) and dimethylformamide (80 ml) is added 5,6-dimethyl-2-phenyl-4(3H)-pyrimidinone (5.0 g) while the temperature of the mixture is kept at 0-5°C, and the mixture is stirred at 0°C for 30 minutes. To the mixture is added dropwise ethyl bromoacetate (4.2 g) at the same temperature. After addition, the mixture is stirred at 80°C for three hours, and thereto are added ice-water and chloroform. The chloroform layer is collected by filtration, washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from isopropanol to give ethyl 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetate (6.2 g), m.p. 90-91°C.
(2) A mixture of the above product (6.0 g), 1N aqueous sodium hydroxide solution (100 ml) and ethanol (50 ml) is stirred at room temperature for 8 hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ice-water. The pH value of the mixture is adjusted to pH 1 with conc. hydrochloric acid, and the precipitates are collected by filtration, washed with water, and recrystallized from ethanol to give the desired compound (3.5 g), m.p. 175-177°C.

Reference Examples 89-90

The corresponding starting compounds are treated in the same manner as in Reference Example 88, and the products thus obtained are recrystallized from ethanol to give the following compounds.

(Reference Example 89)

2-(5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinyloxy)acetic acid; m.p. 155-157°C

(Reference Example 90)

2-[2-(4-Chlorophenyl)-5,6,7,8-tetrahydro-4-quinazolinyloxy)acetic acid; m.p. 195-197°C

Reference Examples 91-92

The corresponding starting t-butoxycarbonylated amino acids are treated in the same manner as in Reference Example 70 to give the following compounds as an oily product.

(Reference Example 91)

2-Methylamino-N-phenyl-N-propylacetamide

(Reference Example 92)

N-Allyl-2-methylamino-N-phenylacetamide

Reference Examples 93-94

The corresponding starting t-butoxycarbonylated amino acids are treated in the same manner as in Reference Example 70-(1) and -(3) to give the following compounds as an oily product.

(Reference Example 93)

N,N-Diethyl-2-methylaminoacetamide

(Reference Example 94)

N-Ethyl-2-methylamino-N-phenylacetamide

Example 1

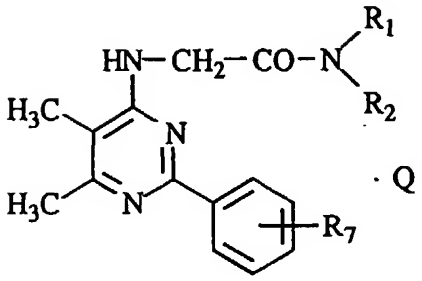
Preparation of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

A mixture of 4-chloro-5,6-dimethyl-2-phenylpyrimidine (1.0 g), 2-amino-N,N-dipropylacetamide (0.87 g) and triethylamine (0.55 g) is refluxed with stirring at 150°C for three hours. To the reaction mixture are added water and chloroform, and the chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound (1.3 g), m.p. 79-80°C.

Examples 2-63

The corresponding starting compounds are treated in the same manner as in Example 1 to give the compounds as listed in Table 13.

Table 13

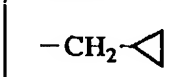
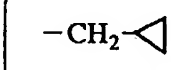


Ex.	R_1	R_2	R_7	Q	M.p. (°C)	Solv. for recrystal.
2	Pr	Pr	4-Cl		74-75	E-HX
3	Pr	Pr	3-Cl		101-103	IP
4	Pr	Pr	4-F		70-71	E-HX
5	Pr	Pr	4-OMe		83-85	IP
6	Pr	Pr	4-CF_3		83-85	HX-EA
7	Pr	Pr	4-NO_2		135-137	IP
8	Me	Me	H		174-175	IP
9	Et	Et	H		113-114	E-HX
10	Et	Et	4-Cl		152-153	IP
11	Et	Et	4-F		139-140	IP
12	Et	Et	4-OMe		130-132	IP
13	i-Pr	i-Pr	H		171-172	IP
14	Bu	Bu	H		46-47	HX
15	Bu	Bu	4-Cl		52-53	HX
16	Bu	Bu	4-F		45-46	HX
17	Et	Pr	H		69-71	E-HX
18	Et	Pr	4-Cl		103-104	HX
19	Et	Pr	4-F		85-86	HX
20	Et	Pr	4-OMe		89-90	HX
21	Me	i-Bu	H		100-102	E-HX
22	Me	Ph	H		145-146	IP
23	Me	Ph	4-Cl		150-152	IP
24	Me	Ph	3-Cl		149-151	IP

Table 13 (continued)

Ex.	R_1	R_2	R_7	Q	M.p. (°C)	Solv. for recrystal.
25	Me	Ph	4-F		146-148	IP
26	Me	Ph	4-OMe		173-174	IP
27	Me	Ph	4-CF_3		192-194	IP
28	Me	Ph	4-NO_2		199-201	AC
29	Me	Ph-4-Cl	H		165-166	IP
30	Me	Ph-2-Cl	H		137-138	IP
31	Me	Ph-3-Cl	H		129-130	IP
32	Me	Ph-4-Cl	4-Cl		170-171	IP
33	Me	Ph-4-Cl	4-F		174-175	IP
34	Me	Ph-4-Cl	4-OMe		157-158	IP
35	Me	Ph-4-F	H	1/4 H_2O	140-142	A
36	Me	Ph-4-F	4-Cl		163-164	A
37	Me	Ph-4-Br	H		183-184	A
38	Me	Ph-4-Br	4-Cl		176-177	IP
39	Me	Ph-4-Br	4-F		184-185	IP
40	Me	Ph-4-Br	4-OMe		168-169	IP
41	Me	Ph-4-OMe	H		166-167	A
42	Me	Ph-4-OMe	4-Cl		173-174	A
43	Me	Ph-4-OMe	4-F		172-173	IP
44	Et	Ph	H		138-139	E
45	Et	Ph	4-Cl		142-143	IP
46	Et	Ph	3-Cl		135-137	IP
47	Et	Ph	4-F		132-133	IP
48	Et	Ph	4-OMe		133-134	IP
49	Et	Ph	4-CF_3		166-167	IP
50	Et	Ph	4-NO_2		180-182	AC
51	Et	Ph-4-Cl	H		194-196	A
52	Pr	Ph	H		148-149	IP

Table 13 (continued)

Ex.	R_1	R_2	R_7	Q	M.p. (°C)	Solv. for recrystal.
53	Pr	Ph	4-Cl		174-175	A
54	Pr	Ph	4-F		164-165	IP
55	Pr	Ph	4-OMe		125-126	IP
56	Pr	Ph-4-Cl	H		167-169	A
57	Bu	Ph	H		134-135	IP
58	$-CH_2CH=CH_2$	Ph	H		125-126	IP
59	$-CH_2CH=CH_2$	Ph	4-Cl		151-152	A
60	$-CH_2CH=CH_2$	Ph	4-OMe		118-119	IP
61		Ph	H		105-106	E-HX
62		Ph	4-Cl		157-158	A
63	H	Ph	H		155-156	E

Examples 64-68

The corresponding starting compounds are treated in the same manner as in Example 1 to give the following compounds.

(Example 64)

N-Cyclohexyl-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetamide; m.p. 112-114°C (recrystallized from n-hexane)

(Example 65)

3,5-Dimethyyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetylpiperidine; m.p. 97-98°C (recrystallized from n-hexane)

(Example 66)

(a) 2,6-Dimethyl-4-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetylmorpholine; m.p. 151-152°C (recrystallized from isopropanol)

(b) cis-2,6-Dimethyl-4-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetylmorpholine;

The compound obtained in Example 29a is purified by silica gel flash column chromatography (eluent; n-hexane:ethyl acetate = 3:1), and the less polar fractions are combined, concentrated under reduced pressure, and recrystallized from isopropanol to give the desired compound, m.p. 162-163°C.

(c) trans-2,6-Dimethyl-4-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetylmorpholine;

The compound obtained in Example 29a is purified by silica gel flash column chromatography (eluent; n-hexane:ethyl acetate = 3:1), and the more polar fractions are combined, concentrated under reduced pressure, and recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound, m.p. 112-113°C.

(Example 67)

cis-3,5-Dimethyl-1-(5,6-dimethyl-2-phenyl-5-pyrimidinylamino)acetylpiperazine; m.p. 134-137°C (recrystallized from a mixture of diethyl ether and n-hexane)

(Example 68)

4-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]acetyl-2,6-dimethylmorpholine; m.p. 212-214°C (recrystallized from isopropanol)

Example 69

Preparation of 3-hydroxy-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylpropanamide:

(1) A mixture of 4-chloro-5,6-dimethyl-2-phenylpyrimidine (1.8 g), 2-amino-3-benzyloxy-N,N-dipropylpropanamide (4.6 g), which is prepared from N-(tert-butoxycarbonyl)-O-benzylserine, and triethylamine (1.7 g) is stirred at 150°C for 5 hours. The reaction mixture is treated in the same manner as in Example 1 to give 3-benzyloxy-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylpropanamide (3.5 g) as an oily product.
(2) A mixture of the above product (3.4 g), acetic acid (50 ml), water (10 ml), ethanol (10 ml) and 10 % palladium-carbon (0.5 g) is stirred at 60°C for five hours under hydrogen atmosphere, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure, and the residue is recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound (2.5 g), m.p. 132-133°C.

Example 70

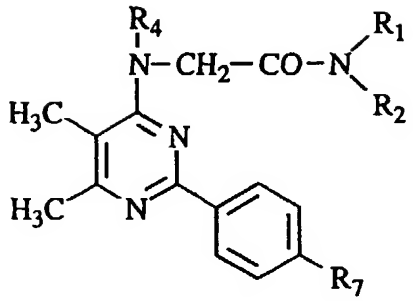
Preparation of 2-[methyl-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)amino]-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 2-methylamino-N,N-dipropylacetamide is used instead of 2-amino-N,N-dipropylacetamide, and to the product thus obtained is added hydrogen chloride isopropanol solution. The precipitated crystals are collected by filtration, and washed with diethyl ether to give a hydrochloride • 1/10 hydrate of the desired compound, m.p. 162-165°C.

Examples 71-78

The corresponding starting compounds are treated in the same manner as in Example 1 to give the compounds as listed in Table 14.

Table 14



Ex.	R_1	R_2	R_4	R_7	M.p. (°C)	Solv. for recrystal.
71	Pr	Pr	Et	Cl	85-86	HX
72	Pr	Pr	Et	OMe	111-112	HX
73	Me	Ph	Me	H	117-119	IP
74	Me	Ph	Me	F	140-141	IP
75	Me	Ph	Me	OMe	151-152	IP
76	Me	Ph-4-Cl	Me	H	114-115	IP
77	Me	Ph	Et	H	107-108	HX
78	Me	Ph	Et	Cl	100-101	HX

Example 79

Preparation of N-(4-chlorophenyl)-N-methyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-2-pyrrolidinecarboxamide:

The same procedures as Example 1 are repeated except that N-(4-chlorophenyl)-N-methyl-2-pyrrolidinecarboxamide is used instead of 2-amino-N,N-dipropylacetamide, and to the product thus obtained is added hydrogen chloride diethyl ether solution. The precipitated crystals are collected by filtration, and washed with diethyl ether to give a hydrochloride of the desired compound, m.p. 119-121°C.

Example 80

Preparation of N-(4-chlorophenyl)-N-methyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-2-piperidinecarboxamide:

The same procedures as Example 1 are repeated except that N-(4-chlorophenyl)-N-methyl-2-piperidinecarboxamide is used instead of 2-amino-N,N-dipropylacetamide. The product thus obtained is recrystallized from a mixture of diethyl ether and n-hexane to give a 1/10 hydrochloride of the desired compound, m.p. 149-151°C.

Example 81

Preparation of 2,3-dihydro-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-N,N-dipropyl-1H-indole-2-carboxamide:

The same procedures as Example 1 are repeated except that 2,3-dihydro-N,N-dipropyl-1H-indole-2-carboxamide is used instead of 2-amino-N,N-dipropylacetamide. The product thus obtained is recrystallized from n-hexane to give a 1/4 hydrate of the desired compound, m.p. 167-168°C.

Example 82

Preparation of N-(4-chlorophenyl)-2,3-dihydro-N-methyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-1H-indole-2-carboxamide:

The same procedures as Example 1 are repeated except that N-(4-chlorophenyl)-2,3-dihydro-N-methyl-1H-indole-2-carboxamide is used instead of 2-amino-N,N-dipropylacetamide. The product thus obtained is recrystallized from methanol to give a 1/10 hydrochloride • 1/4 hydrate of the desired compound, m.p. 236-238°C.

Example 83

Preparation of 2-(5-ethyl-6-methyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-5-ethyl-6-methyl-2-phenylpyrimidine is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound, m.p. 83-84°C.

Example 84

Preparation of N-(4-chlorophenyl)-2-(5-ethyl-6-methyl-2-phenyl-4-pyrimidinylamino)-N-methylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-5-ethyl-6-methyl-2-phenylpyrimidine and 2-amino-N-(4-chlorophenyl)-N-methylacetamide are used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine and 2-amino-N,N-dipropylacetamide, respectively. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 142-143°C.

Example 85

Preparation of 2-(6-ethyl-5-methyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-6-ethyl-5-methyl-2-phenylpyrimidine is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound, m.p. 83-84°C.

Example 86

Preparation of 2-(6-isopropyl-5-methyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-6-isopropyl-5-methyl-2-phenylpyrimidine is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound, m.p. 98-99°C.

Example 87

Preparation of 2-(6-methyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-6-methyl-2-phenylpyrimidine is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from diethyl ether to give the desired compound, m.p. 107-108°C.

Example 88

Preparation of 2-(6-methyl-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-6-methyl-2-phenylpyrimidine and 2-amino-N-methyl-N-phenylacetamide are used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine and 2-amino-N,N-dipropylacetamide, respectively. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 134-136°C.

Example 89

Preparation of 2-(5-chloro-6-methyl-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide:

A mixture of 2-(6-methyl-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide (1.0 g) obtained in Example 88, N-chlorosuccinimide (0.44 g) and acetic acid (15 ml) is heated with stirring at 90°C for three hours, and the reaction mixture is concentrated under reduced pressure. To the residue is added ice-water (30 ml) with stirring, and the precipitates are collected by filtration, washed with water, and recrystallized from isopropanol to give the desired compound (1.1 g), m.p. 154-155°C.

Example 90

Preparation of 2-(5-bromo-6-methyl-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide:

The same procedures as Example 89 are repeated except that N-bromosuccinimide is used instead of N-chlorosuccinimide. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 160-162°C.

Example 91

Preparation of 2-(2-phenyl-6-trifluoromethyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-6-trifluoromethyl-2-phenylpyrimidine is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 128-130°C.

Example 92

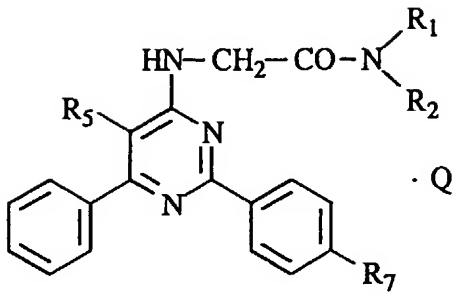
Preparation of 2-(5-chloro-2-phenyl-6-trifluoromethyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 89 are repeated except that 2-(2-phenyl-6-trifluoromethyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide is used instead of 2-(6-methyl-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 115-117°C.

Examples 93-99

The corresponding starting compounds are treated in the same manner as in Example 1 to give the compounds as listed in Table 15.

Table 15



Ex.	R_1	R_2	R_5	R_7	Q	M.p. (°C)	Solv. for recrystal.
93	Pr	Pr	H	H		102-103	E-HX
94	Pr	Pr	H	Cl		146-148	IP
95	Me	Ph	H	Cl	1/10 HCl	180-181	A
96	Me	Ph-4-Cl	H	H	1/4 H_2O	157-158	IP
97	Pr	Pr	Me	H		139-140	IP
98	Pr	Pr	Me	Cl		129-130	IP
99	Me	Ph	Me	H		146-147	IP

Example 100

Preparation of 3,5-dimethyl-1-(2,6-diphenyl-4-pyrimidinylamino)acetylpiperidine:

The same procedures as Example 1 are repeated except that 4-chloro-2,6-diphenylpyrimidine and 1-aminoacetyl-3,5-dimethylpiperidine are used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine and 2-amino-N,N-dipropylacetamide, respectively. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 134-135°C.

Example 101

Preparation of 2-(2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-2-phenylpyrimidine, which is prepared according to the method disclosed in Rec. Trav. Chim. Pays-Bas, 86, 15 (1967), is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from diethyl ether to give the desired compound, m.p. 74-75°C.

Example 102

Preparation of 2-(5,6,7,8-tetrahydro-2-phenyl-4-quinazolinylamino)-N,N-dipropylacetamide:

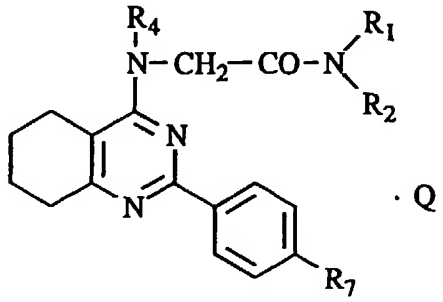
A mixture of 4-chloro-5,6,7,8-tetrahydro-2-phenylquinazoline (1.0 g), 2-amino-N,N-dipropylacetamide (0.78 g) and triethylamine (0.5 g) is refluxed with stirring at 150°C for three hours. To the reaction mixture are added water and chloroform, and the chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from a

mixture of diethyl ether and n-hexane to give the desired compound (1.3 g), m.p. 87-88°C.

Examples 103-112

The corresponding starting compounds are treated in the same manner as in Example 102 to give the compounds as listed in Table 16.

Table 16

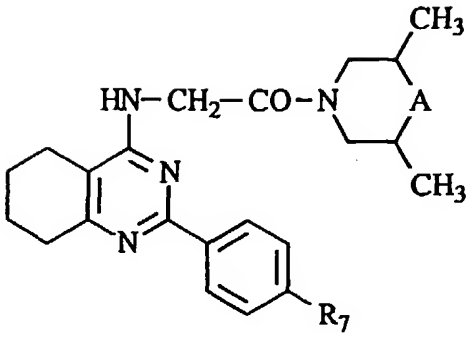


Ex.	R_1	R_2	R_4	R_7	Q	M.p. (°C)	Solve. for recrystal.
103	Pr	Pr	H	F		88-89	HX
104	Pr	Pr	H	Cl		98-99	E-HX
105	Bu	Bu	H	H		71-72	HX
106	Bu	Bu	H	F		65-66	HX
107	Bu	Bu	H	Cl		83-84	HX
108	Me	Ph-4-Cl	H	H		225-227	M
109	Me	Ph-4-Cl	H	Cl		177-178	IP
110	Pr	Pr	Me	H	HCl, 3/4 H_2O	154-156	IP
111	Me	Ph-4-Cl	Me	H	1/10 HCl	176-177	IP
112	Me	Ph-4-Cl	Me	F		139-140	IP

Examples 113-117

The corresponding starting compounds are treated in the same manner as in Example 102 to give the compounds as listed in Table 17.

Table 17



Ex.	A	R_7	M.p. (°C)	Solv. for recrystal.
113	O	H	164-165	IP
114	O	F	212-214	A
115	O	Cl	225-227	A
116	NH	H	178-179	IP
117	NH	F	195-197	IP

Example 118

Preparation of 3-hydroxy-2-(5,6,7,8-tetrahydro-2-phenyl-4-quinazolinylamino)-N,N-dipropylpropanamide:

(1) The same procedures as Example 102 are repeated except that 2-amino-3-benzyloxy-N,N-dipropylpropanamide (4.1 g) is used instead of 2-amino-N,N-dipropylacetamide to give 3-benzyloxy-2-(5,6,7,8-tetrahydro-2-phenyl-4-quinazolinylamino)-N,N-dipropylpropanamide (3.4 g) as an oily product.
(2) A mixture of the above product (3.0 g), acetic acid (100 ml) and 10 % palladium-carbon (1.0 g) is stirred at 60°C for six hours under hydrogen atmosphere, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure and recrystallized from diethyl ether to give the desired compound (2.0 g), m.p. 119-120°C.

Examples 119-120

Instead of 2-amino-N,N-dipropylacetamide, the corresponding starting compounds are treated in the same manner as in Example 102 to give the following compounds.

(Example 119)

1-(5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinyl)-N,N-dipropyl-2-pyrrolidinecarboxamide; m.p. 123-124°C (recrystallized from diethyl ether)

(Example 120)

N-(4-Chlorophenyl)-1-(5,6,7,8-tetrahydro-2-phenyl-4-quinazolinyl)-N-methyl-2-pyrrolidinecarboxamide • 1/4 hydrate; m.p. 80-82°C (recrystallized from n-hexane)

Example 121

Preparation of 2-(5-nitro-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

A mixture of 4-chloro-5-nitro-2-phenylpyrimidine (6.0 g), 2-amino-N,N-dipropylacetamide (6.0 g), triethylamine (5.2 g) and isopropanol (70 ml) is refluxed for six hours. The reaction mixture is concentrated under reduced pressure, and to the residue are added chloroform and water. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (8.8 g), m.p. 142-143°C.

Example 122

Preparation of 2-(5-amino-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;

A mixture of 2-(5-nitro-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide (1.9 g) obtained in Example 121, ethanol (60 ml) and 10 % palladium-carbon (0.2 g) is stirred at room temperature for three hours under hydrogen atmosphere, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure, and recrystallized from diethyl ether to give the desired compound (1.5 g), m.p. 120-122°C.

Example 123

Preparation of N-methyl-2-(5-nitro-2-phenyl-4-pyrimidinylamino)-N-phenylacetamide:

The same procedures as Example 121 are repeated except that 2-amino-N-methyl-N-phenylacetamide (7.3 g) is used instead of 2-amino-N,N-dipropylacetamide. The product thus obtained is recrystallized from ethanol to give the desired compound (10.1 g), m.p. 194-196°C.

Example 124

Preparation of 2-(5-amino-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide:

2-(5-Nitro-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide (5.5 g) obtained in Example 123 is treated in the same manner as in Example 122, and the product thus obtained is recrystallized from ethanol to give a 1/4 hydrate of the desired compound (4.8 g), m.p. 183-184°C.

Example 125

Preparation of 2-(5-acetylamino-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide:

A mixture of 2-(5-amino-2-phenyl-4-pyrimidinylamino)-N-methyl-N-phenylacetamide (3.6 g) obtained in Example 124, acetic anhydride (10 ml) and pyridine (7 ml) is stirred at room temperature for four hours. To the reaction mixture is added chloroform, and the mixture is washed with 1N hydrochloric acid, then washed with a saturated aqueous sodium hydrogen carbonate solution. The chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (4.0 g), m.p. 200-201°C.

Example 126

Preparation of 2-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

The same procedures as Example 1 are repeated except that 4-chloro-5-ethoxycarbonyl-2-phenylpyrimidine (6.0 g) is used instead of 4-chloro-5,6-dimethyl-2-phenylpyrimidine. The product thus obtained is recrystallized from n-hexane to give the desired compound, m.p. 45-46°C.

Example 127

Preparation of 2-(5-hydroxymethyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide:

To a mixture of 2-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinylamino)-N,N-dipropylacetamide (3.0 g) obtained in Example 126, sodium borohydride (0.6 g), lithium chloride (0.7 g) and tetrahydrofuran (20 ml) is added dropwise anhydrous ethanol (30 ml) at 0 to 5°C. The reaction mixture is stirred at room temperature for five hours, and the pH value thereof is adjusted to pH 5 with 1N hydrochloric acid, and concentrated under reduced pressure. To the residue are added a brine and chloroform, and the chloroform layer is collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from isopropanol to give the desired compound (2.0 g), m.p. 167-168°C.

Example 128

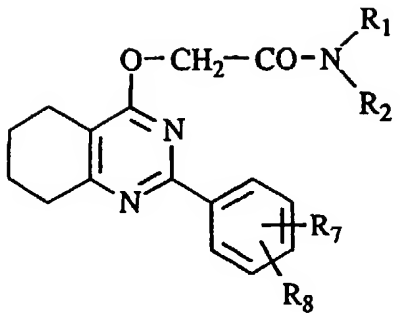
Preparation of 2-[2-(4-fluorophenyl)-5,6,7,8-tetrahydro-4-quinazolinyloxy]-N,N-dipropylacetamide:

To a mixture of 2-hydroxy-N,N-dipropylacetamide (1.8 g) and dimethylformamide (20 ml) is added sodium hydride (about 60 % oily, 0.5 g) at 0 to 5°C, and the mixture is stirred at 0°C for one hour. To the reaction mixture is added 4-chloro-2-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (2.0 g) at the same temperature, and the mixture is stirred at room temperature for four hours. To the mixture are added chloroform and ice-water, and the chloroform layer is collected, washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from a mixture of diethyl ether and n-hexane to give the desired compound (2.2 g), m.p. 95-96°C.

Examples 129-135

The corresponding starting compounds are treated in the same manner as in Example 128 to give the compounds as listed in Table 18.

Table 18



Ex.	R_1	R_2	R_7	R_8	M.p. (°C)	Solv. for recrystal.
129	Pr	Pr	2-Cl	H	75-76	HX
130	Pr	Pr	3-Cl	H	100-101	HX
131	Pr	Pr	4-Cl	H	119-120	IP
132	Pr	Pr	2-F	4-F	93-94	HX
133	Bu	Bu	H	H	84-85	HX
134	Bu	Bu	4-F	H	90-91	HX
135	Bu	Bu	4-Cl	H	105-106	IP

Example 136

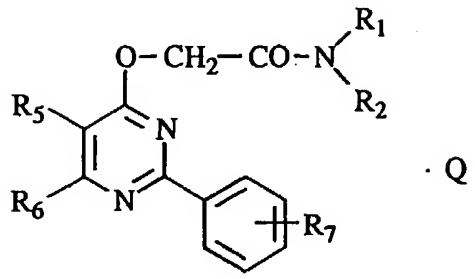
Preparation of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide:

To a mixture of 5,6-dimethyl-2-phenyl-4-(3H)-pyrimidinone (1.5 g) and dimethylformamide (20 ml) is added sodium hydride (about 60 % oily, 0.3 g) at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added 2-bromo-N,N-dipropylacetamide (1.67 g) at the same temperature, and the mixture is stirred at room temperature for two hours. To the reaction mixture are added chloroform and ice-water, and the chloroform layer is collected, washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from n-hexane to give the desired compound (2.2 g), m.p. 88-89°C.

Examples 137-163

The corresponding starting compounds are treated in the same manner as in Example 136 to give the compounds as listed in Table 19.

Table 19



· Q

Ex.	R_5	R_6	R_1	R_2	R_7	Q	M.p. (°C)	Solve. for recrystal.
137	Me	Me	Pr	Pr	4-Cl		128-130	E-HX
138	Me	Me	Pr	Pr	4-F		131-133	A
139	Me	Me	Pr	Pr	4-OMe		87-88	HX
140	Me	Me	Pr	Pr	3-Cl		82-84	E-HX
141	Me	Me	Pr	Pr	4-CF_3		109-111	HX
142	Me	Me	Pr	Pr	4-NO_2		157-159	M
143	Me	Me	Me	Ph	H		138-139	IP
144	Me	Me	Me	Ph	4-Cl		159-161	A
145	Me	Me	Me	Ph	3-Cl		170-173	IP
146	Me	Me	Me	Ph	4-OMe		157-159	IP
147	Me	Me	Me	Ph	4-CF_3		159-161	IP
148	Me	Me	Me	Ph	4-NO_2		179-181	AC
149	Me	Me	Me	Ph-4-Cl	H		168-170	IP
150	Me	Me	Me	Ph-4-Cl	4-OMe		142-143	A
151	Me	Me	Et	Ph	H		130-132	IP
152	Me	Me	Et	Ph	4-Cl		170-171	A
153	Me	Me	Et	Ph	3-Cl		151-153	IP
154	Me	Me	Et	Ph	4-F		156-158	IP

Table 19 (continued)

Ex.	R_5	R_6	R_1	R_2	R_7	Q	M.p. (°C)	Solve. for recrystal.
155	Me	Me	Et	Ph	4-CF_3		148-150	IP
156	Et	Me	Me	Ph-4-Cl	H		100-101	E-HX
157	Me	Et	Pr	Pr	H		62-63	HX
158	H	Ph	Pr	Pr	H		82-83	E
159	Me	Ph	Pr	Pr	H		78-79	HX
160	H	CF_3	Pr	Pr	H		109-110	IP
161	-$(CH_2)_4$-		Pr	Pr	H		92-93	E-HX
162	-$(CH_2)_4$-		Me	Ph-4-Cl	H		140-141	IP
163	-$(CH_2)_4$-		Me	Ph-4-Cl	4-Cl	1/4 H_2O	200-202	A

Example 164

Preparation of N-ethyl-2-[5,6-dimethyl-2-(4-nitrophenyl)-4-pyrimidinyloxy]-N-phenylacetamide:

The same procedures as Example 136 are repeated except that 5,6-dimethyl-2-(4-nitrophenyl)-4-(3H)-pyrimidinone and 2-bromo-N-ethyl-N-phenylacetamide are used instead of 5,6-dimethyl-2-phenyl-4-(3H)-pyrimidinone and 2-bromo-N,N-dipropylacetamide, respectively. The product thus obtained is recrystallized from acetonitrile to give the desired compound, m.p. 189-190°C.

Example 165

Preparation of 2-[2-(4-aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide:

A mixture of 2-[5,6-dimethyl-2-(4-nitrophenyl)-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide (2.3 g) obtained in Example 164, 5 % palladium-carbon (0.4 g), ethanol (30 ml) and chloroform (10 ml) is stirred at room temperature for three hours under hydrogen atmosphere, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure, and recrystallized from acetonitrile to give a 1/10 hydrate of the desired compound (2.1 g), m.p. 183-185°C.

Example 166

Preparation of 2-(6-methyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide:

The same procedures as Example 136 are repeated except that 6-methyl-2-phenyl-4-(3H)-pyrimidinone is used instead of 5,6-dimethyl-2-phenyl-4-(3H)-pyrimidinone. The product thus obtained is recrystallized from n-hexane to give the desired compound, m.p. 68-69°C.

Example 167

Preparation of 2-(5-chloro-6-methyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide:

2-(6-Methyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide obtained in Example 166 is treated in the same manner as in Example 89, and the product is recrystallized from isopropanol to give the desired compound, m.p. 90-91°C.

Example 168

Preparation of 2-(5-bromo-6-methyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide:

2-(6-Methyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide obtained in Example 166 is treated in the same manner as in Example 90, and the product is recrystallized from isopropanol to give the desired compound, m.p. 107-108°C.

Example 169

Preparation of 2-(5,6,7,8-tetrahydro-2-phenyl-4-quinazolinyloxy)-N,N-dipropylpropanamide:

The same procedures as Example 136 are repeated except that 5,6,7,8-tetrahydro-2-phenyl-4-(3H)-quinazolinone and 2-bromo-N,N-dipropylpropanamide are used instead of 5,6-dimethyl-2-phenyl-4-(3H)-pyrimidinone and 2-bromo-N,N-dipropylacetamide, respectively. The product thus obtained is recrystallized from n-hexane to give the desired compound, m.p. 73-74°C.

Example 170

Preparation of 3,5-dimethyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetylpiperidine:

To a mixture of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetic acid (1.2 g), 3,5-dimethylpiperidine (0.7 g), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium • hexafluorophosphate (BOP reagent; 2.26 g) and dimethylformamide (20 ml) is added triethylamine (0.52 g) at 0-5°C, and the mixture is stirred at room temperature for six hours. To the reaction mixture are added chloroform and ice-water, and the chloroform layer is collected, washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from n-hexane to give the desired compound (1.4 g), m.p. 100-101°C.

Examples 171-173

Instead of 3,5-dimethylpiperidine, the corresponding starting compounds are treated in the same manner as in Example 170 to give the following compounds.

(Example 171)

2,6-Dimethyl-4-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetylmorpholine; m.p. 123-124°C (recrystallized from isopropanol)

(Example 172)

3,5-Dimethyl-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetylpiperazine • 1/4 hydrate; m.p. 107-110°C (recrystallized from a mixture of diethyl eter and n-hexane)

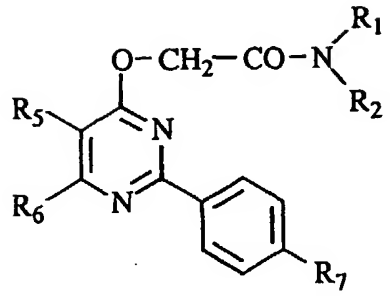
(Example 173)

2,3-Dihydro-1-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)acetyl-1H-indole; m.p. 210-212°C (recrystallized from acetonitrile)

Examples 174-188

The corresponding starting compounds are treated in the same manner as in Example 170 to give the compounds as listed in Table 20.

Table 20



Ex.	R_5	R_6	R_1	R_2	R_7	M.p. (°C)	Solv. for recrystal.
174	Me	Me	Me	Me	H	128-129	IP
175	Me	Me	Et	Et	H	88-90	E-HX
176	Me	Me	Et	Et	Cl	148-149	IP
177	Me	Me	Bu	Bu	H	99-100	E-HX
178	Me	Me	Pr	Ph	H	151-152	IP
179	-$(CH_2)_4$-		Et	Et	H	100-101	E-HX
180	-$(CH_2)_4$-		Me	Ph	H	135-137	IP
181	-$(CH_2)_4$-		Me	Ph	Cl	148-150	IP
182	-$(CH_2)_4$-		Pr	Ph	H	158-160	IP
183	-$(CH_2)_4$-		H	Ph-4-F	H	178-179	M
184	-$(CH_2)_4$-		Me	Ph-4-F	H	164-165	IP
185	-$(CH_2)_4$-		H	Ph-4-Cl	H	179-180	A
186	-$(CH_2)_4$-		Me	Ph-2-Cl	H	165-166	A
187	-$(CH_2)_4$-		Me	Ph-3-Cl	H	180-182	A
188	-$(CH_2)_4$-		Me	CH_2Ph	H	91-92	E

Example 189

Preparation of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenylacetamide:

The same procedures as Example 170 are repeated except that aniline is used instead of 3,5-dimethylpiperidine. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 212-213°C.

Example 190

Preparation of N-cyclopropylmethyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenylacetamide:

To a mixture of 2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenylacetamide (1.5 g) obtained in Example 189 and dimethylformamide (30 ml) is added sodium hydride (about 60 % oily, 0.2 g) at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added cyclopropylmethyl bromide (0.67 g) at the same temperature, and the mixture

is stirred at room temperature for two hours. To the reaction solution are added chloroform and ice-water, and the chloroform layer is collected, washed with water, and dried over anhydrous sodium sulfate. The chloroform layer is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from isopropanol to give the desired compound (1.56 g), m.p. 119-121°C.

Example 191

Preparation of N-allyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenylacetamide:

The same procedures as Example 190 are repeated except that allyl bromide is used instead of propylmethyl bromide. The product thus obtained is recrystallized from isopropanol to give the desired compound, m.p. 129-131°C.

Examples 192-196

The corresponding starting compounds are treated in the same manner as in Example 170 to give the following compounds.

(Example 192)

1-(5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinyloxy)acetyl-3,5-dimethylpiperidine; m.p. 134-135°C (recrystallized from diethyl ether)

(Example 193)

4-(5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinyloxy)acetyl-2,6-dimethylmorpholine; m.p. 161-163°C (recrystallized from isopropanol)

(Example 194)

1-(5,6,7,8-Tetrahydro-2-phenyl-4-quinazolinyloxy)acetyl-cis-3,5-dimethylpiperazine • 1/4 hydrate; m.p. 150-151°C (recrystallized from diethyl ether)

(Example 195)

4-[2-(4-Chlorophenyl)-5,6,7,8-tetrahydro-4-quinazolinyloxy]acetyl-2,6-dimethylmorpholine; m.p. 171-173°C (recrystallized from isopropanol)

(Example 196)

1-[2-(4-Chlorophenyl)-5,6,7,8-tetrahydro-4-quinazolinyloxy]acetyl-cis-3,5-dimethylpiperazine • 9/10 hydrochloride; m.p. 265-268°C (recrystallized from ethanol)

Example 197

Preparation of cis-3,5-dimethyl-1-[(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-2-pyrrolidinylcarbonyl]piperazine:

(1) The same procedures as Example 1 are repeated except that proline benzyl ester hydrochloride (4.0 g) is used instead of 2-amino-N,N-dipropylacetamide. The product thus obtained is recrystallized from isopropanol to give 1-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)-2-pyrrolidinecarboxylic acid (4.0 g), m.p. 90-92°C.

(2) A mixture of the above product (3.8 g), ethanol (100 ml) and 10 % palladium-carbon (1.0 g) is stirred at room temperature for 8 hours under hydrogen atmosphere, and the mixture is filtered. The filtrate is concentrated under reduced pressure, and recrystallized from isopropanol to give N-(5,6-dimethyl-2-phenyl-4-pyrimidinyl)proline (2.5 g), m.p. 228-231°C.

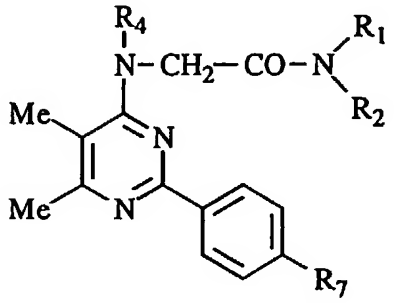
(3) To a mixture of the above product (1.2 g), cis-3,5-dimethylpiperazine (0.6 g), BOP reagent (1.97 g) and dimethylformamide (30 ml) is added triethylamine (0.52 g) at 0-5°C, and the mixture is stirred at room temperature for five hours. To the reaction mixture are added chloroform and ice-water, and the chloroform layer is collected, washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from diethyl ether to give a 1/2 hydrate

of the desired compound (1.4 g), m.p. 160-162°C.

Examples 198-204

The corresponding starting compounds are treated in the same manner as in Example 1 to give the compounds as listed in Table 21.

Table 21



Ex.	R_1	R_2	R_4	R_7	M.p. (°C)	Solv. for recrystal.
198	Et	Et	Me	Cl	131-132	IP
199	Pr	Pr	Me	Cl	84-86	HX
200*	Me	Ph	Me	Cl	139-140	IP
201	Et	Ph	Me	Cl	102-103	HX
202	Pr	Ph	Me	Cl	103-104	HX
203	$-CH_2CH=CH_2$	Ph	Me	Cl	107-108	HX
204	H	Ph	H	Cl	205-206	A

*: 1/4 Hydrate

Example 205

Preparation of 1-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyl]-N-(4-chlorophenyl)-N-methyl-2-pyrrolidinecarboxamide:

The corresponding starting compounds are treated in the same manner as in Example 1, and the product thus obtained is recrystallized from isopropanol to give the title compound, m.p. 131-133°C.

Preparation 1: Preparation of tablets:

2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide	1 g
Lactose	84 g
Corn starch	30 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	3 g
Light anhydrous silicic acid	0.7 g
Magnesium stearate	1.3 g

The above components are mixed and kneaded in a conventional manner, and the mixture is granulated, and the resultants are further tabletted to give 1,000 tablets (each 145 mg).

Preparation 2: Preparation of tablets

2-[5,6-Dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide	25 g
Lactose	70 g
Corn starch	20 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	3 g
Light anhydrous silicic acid	0.7 g
Magnesium stearate	1.3 g

The above components are mixed and kneaded in a conventional manner, and the mixture is granulated, and the resultants are further tabletted to give 1,000 tablets (each 145 mg).

Preparation 3: Preparation of capsules

2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-dipropylacetamide	2 g
Lactose	165 g
Corn starch	25 g
Hydroxypropyl cellulose	3.5 g
Light anhydrous silicic acid	1.8 g
Magnesium stearate	2.7 g

The above components are mixed and kneaded in a conventional manner, and the mixture is granulated, and each 200 mg of the resultant is packed into a capsule to give 1,000 capsules.

Preparation 4: Preparation of powder

N-(4-Chlorophenyl)-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetamide	10 g
Lactose	960 g
Hydroxypropyl cellulose	25 g
Light anhydrous silicic acid	5 g

The above components are mixed to give powder preparation.

Preparation 5: Preparation of injection preparation

2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide		10 g
Ethanol		200 g
HCO-60		2 g
Citric acid		10 g
Sorbitol		50 g
Sodium hydroxide		q.s.
Distilled water for injection		q.s
	Totally	2000 ml

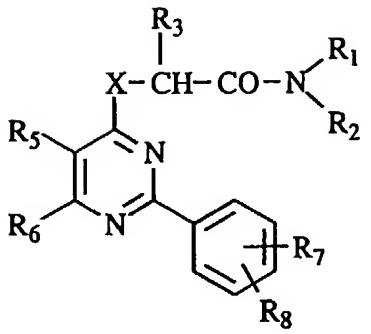
2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide is dissolved in a mixture of ethanol and HCO-60, and thereto is added a suitable amount of distilled water for injection, and further thereto are added citric acid and sorbitol. The pH value of the mixture is adjusted to pH 4.5 with sodium hydroxide, and the total amount of the mixture is controlled with addition of distilled water for injection. The solution thus obtained is filtered on a membrane filter (0.22 μm), and the filtrate is put into ampules (capacity; 2 ml), and the ampules are sterilized at 121°C for 20 minutes.

INDUSTRIAL APPLICABILITY

As explained above, the present compounds of the formula (I) or a pharmaceutically acceptable acid addition salt thereof show a selective and remarkable affinity for the peripheral-type BZ ω_3-receptor as well as show excellent pharmacological activities such as anxiolytic activity, antiepileptic activity, etc. in animal tests, and hence, they are useful in the prophylaxis or treatment of central nervous disorders such as anxiety-related diseases (neurosis, somatoform disorders, other anxiety disorders), depression, epilepsy, etc., or circulatory organs disorders such as angina pectoris, hypertension, etc. Besides, the present compounds of the formula (I) and a pharmaceutically acceptable acid addition salt thereof can be expected to be useful in the prophylaxis or treatment of immuno neurological disorders such as multiple sclerosis, and immuno inflammatory diseases such as rheumatoid arthritis.

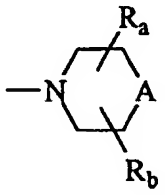
Claims

1. An acetamide derivative of the formula (I):



(I)

wherein X is —O— or —NR_4—,
R_1 is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a cyclolalkyl-lower alkyl group,
R_2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, or R_1 and R_2 may optionally combine together with the nitrogen atom to which they are attached to form a group of the formula:



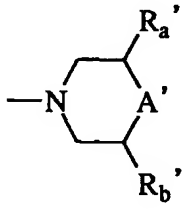
wherein A is a single bond, —CH_2—, —O— or —NH—, R_a and R_b are the same or different and each a hydrogen atom or a lower alkyl group, or when A is a single bond, and R_a and R_b are located at the 2-position and the 3-position, respectively, the carbon atoms of the 2-position and the 3-position and R_a and R_b may optionally combine to form a phenyl ring,

R_3 is a hydrogen atom, a lower alkyl group or a hydroxy-lower alkyl group,
R_4 is a hydrogen atom or a lower alkyl group, or R_3 and R_4 may optionally combine together with the carbon atom and the nitrogen atom to which they are attached to form pyrrolidine, piperidine, or 2,3-dihydro-1H-indole ring,
R_5 is a hydrogen atom, a lower alkyl group, a lower alkenyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted benzyloxy-lower alkyl group, an acyloxy-lower alkyl group, a lower alkoxy-lower alkyl group, a trifluoromethyl group, a halogen atom, an amino group, a mono- or di-lower alkylamino group, an acylamino group, an amino-lower alkyl group, a nitro group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a carboxyl group, a protected carboxyl group, a carboxy-lower alkyl group or a protected carboxy-lower alkyl group,
R_6 is a hydrogen atom, a lower alkyl group, a trifluoromethyl group or a substituted or unsubstituted phenyl group, or R_5 and R_6 may optionally combine to form —$(CH_2)_n$— (n is 3, 4, 5 or 6),
R_7 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group or a nitro group,
R_8 is a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group,
or a pharmaceutically acceptable acid addition salt thereof.

2. The compound according to claim 1, wherein R_5 is a hydrogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a halogen atom, an amino group, an acylamino group, a nitro group or a protected carboxyl group.

3. The compound according to claim 1, wherein R_1 and R_2 are the same or different and each a lower alkyl group, or

R_1 is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group, and R_2 is a substituted or unsubstituted phenyl group, or R_1 and R_2 may optionally combine together with the nitrogen atom to which they are attached to form a group of the formula:

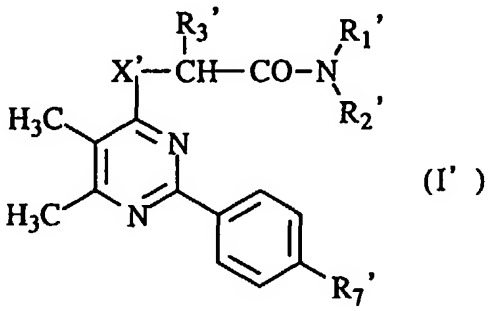


wherein A' is —CH_2— or —O—, and R_a' and R_b' are the same or different and each a lower alkyl group, and R_5 is a hydrogen atom, a lower alkyl group, a hydroxy-lower alkyl group, a halogen atom, an amino group, an acylamino group, a nitro group or a protected carboxyl group.

4. The compound according to claim 1, wherein R_1 and R_2 are the same or different and each a methyl group, an ethyl group, a propyl group, an isopropyl group or a butyl group, or R_1 is a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an allyl group or a cyclopropylmethyl group, and R_2 is a phenyl group or a phenyl group being substituted by a halogen atom or a methoxy group, R_3 is a hydrogen atom, R_5 is a hydrogen atom, a methyl group, an ethyl group or a hydroxymethyl group, R_6 is a methyl group or a phenyl group, or R_5 and R_6 may optionally combine to form —$(CH_2)_4$—, R_7 is a hydrogen atom, a halogen atom, a C_1-C_3 alkoxy group, a trifluoromethyl group, an amino group or a nitro group, and R_8 is a hydrogen atom.

5. The compound according to claim 4, wherein X is —O— or —NR_4'—, R_1 and R_2 are the same or different and each an ethyl group, a propyl group or a butyl group, or R_1 is a methyl group, an ethyl group, a propyl group, an allyl group or a cyclopropylmethyl group, and R_2 is a phenyl group, a halogenophenyl group or a methoxyphenyl group, R_3 is a hydrogen atom, R_4' is a hydrogen atom, a methyl group or an ethyl group, or R_3 and R_4' may optionally combine together with the carbon atom and the nitrogen atom to which they are attached to form a pyrrolidine ring or a 2,3-dihydro-1H-indole ring, R_7 is a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl group, an amino group or a nitro group, and R_8 is a hydrogen atom.

6. An acetamide derivative of the formula (I'):



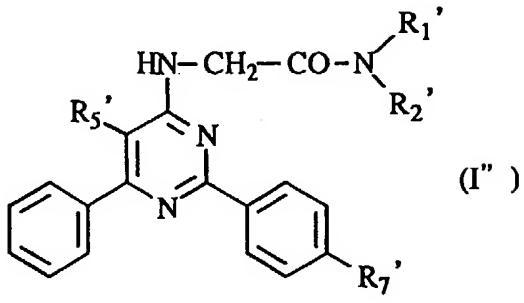
(I')

wherein X' is —O— or —NR_4"—, R_1' and R_2' are both an ethyl group or a propyl group, or R_1' is a methyl group, an ethyl group, a propyl group, an allyl group or a cyclopropylmethyl group, R_2' is a phenyl group or a 4-halogenophenyl group, or a 4-methoxyphenyl group, R_3' is a hydrogen atom, R_4" is a hydrogen atom, a methyl group, or an ethyl group, R_7' is a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl group, an amino group or a nitro group, or a pharmaceutically acceptable acid addition salt thereof.

7. The compound according to claim 6, wherein X' is —NH—.

8. The compound according to claim 6, wherein X' is —O—.

9. An acetamide derivative of the formula (I"):



(I")

wherein R_1' and R_2' are both an ethyl group or a propyl group, or R_1' is a methyl group, an ethyl group, a propyl group, an allyl group or a cyclopropylmethyl group, R_2' is a phenyl group or a 4-halogenophenyl group or a 4-methoxyphenyl group, R_5' is a hydrogen atom, a methyl group or an ethyl group, R_7' is a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl group, an amino group or a nitro group, or a pharmaceutically acceptable acid addition salt thereof.

10. A compound which is selected from the following compounds:

2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-diethylacetamide;
N-(4-chlorophenyl)-N-methyl-2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)acetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-fluorophenyl)-N-methylacetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-(4-methoxyphenyl)-N-methylacetamide;
2-(5,6-dimethyl-2-phenyl-4-pyrimidinylamino)-N-phenyl-N-propylacetamide: and
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-ethyl-N-phenylacetamide,
or a pharmaceutically acceptable acid addition salt thereof.

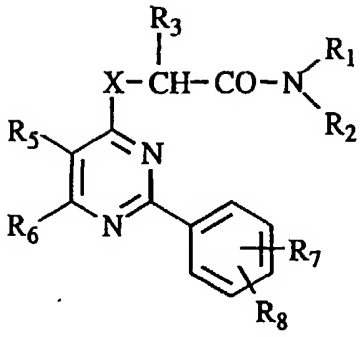
11. A compound which is selected from the following compounds:

2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide;
2-(2,6-diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;
2-[5,6-dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide;
N-ethyl-2-[5,6-dimethyl-2-(4-aminophenyl)-4-pyrimidinyloxy]-N-phenylacetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-methyl-N-phenylacetamide; and
2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide,
or a pharmaceutically acceptable acid addition salt thereof.

12. 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N,N-dipropylacetamide, or a pharmaceutically acceptable acid addition salt thereof.

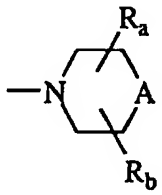
13. 2-[2-(4-Chlorophenyl)-5,6-dimethyl-4-pyrimidinylamino]-N-methyl-N-phenylacetamide, or a pharmaceutically acceptable acid addition salt thereof.

14. A process for preparing an acetamide derivative of the formula (I):



(I)

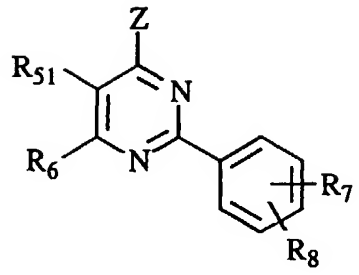
wherein X is —O— or —NR_4—,
R_1 is a hydrogen atom, a lower alkyl group, a lower alkenyl group or a cyclolalkyl-lower alkyl group,
R_2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, or R_1 and R_2 may optionally combine together with the nitrogen atom to which they are attached to form a group of the formula:



wherein A is a single bond, —CH_2—, —O— or —NH—, R_a and R_b are the same or different and each a hydrogen atom or a lower alkyl group, or when A is a single bond, and R_a and R_b are located at the 2-position and the 3-position, respectively, the carbon atoms of the 2-position and the 3-position and R_a and R_b may optionally combine to form a phenyl ring,

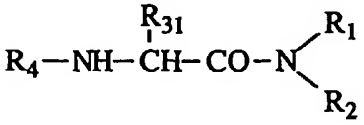
R_3 is a hydrogen atom, a lower alkyl group or a hydroxy-lower alkyl group,
R_4 is a hydrogen atom or a lower alkyl group, or R_3 and R_4 may optionally combine together with the carbon atom and the nitrogen atom to which they are attached to form a pyrrolidine, a piperidine, or a 2,3-dihydro-1H-indole ring,
R_5 is a hydrogen atom, a lower alkyl group, a lower alkenyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted benzyloxy-lower alkyl group, an acyloxy-lower alkyl group, a lower alkoxy-lower alkyl group, a trifluoromethyl group, a halogen atom, an amino group, a mono- or di-lower alkylamino group, an acylamino group, an amino-lower alkyl group, a nitro group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a carboxyl group, a protected carboxyl group, a carboxy-lower alkyl group or a protected carboxyl-lower alkyl group,
R_6 is a hydrogen atom, a lower alkyl group, a trifluoromethyl group or a substituted or unsubstituted phenyl group, or R_5 and R_6 may optionally combine to form —$(CH_2)_n$— (n is 3, 4, 5 or 6),
R_7 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group or a nitro group,
R_8 is a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group,
or a pharmaceutically acceptable acid addition salt thereof, which comprises the following processes (a), (b), (c), (d), or (e):

(a): when the compound (I) is a compound of the formula (I) wherein X is —NR_4—, reacting a compound of the formula (II):



(II)

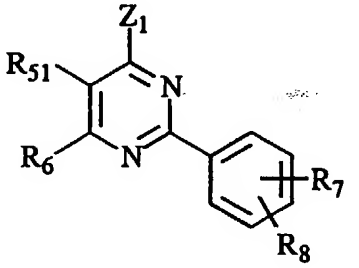
wherein Z is a leaving atom or a leaving group, R_{51} is the same groups as defined above for R_5 except that a hydroxy-lower alkyl group, an amino group, an amino-lower alkyl group, a carboxyl group and a carboxy-lower alkyl group are protected ones, and R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (III):



(III)

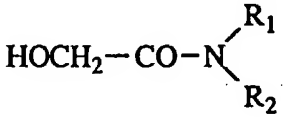
wherein R_{31} is a hydrogen atom, a lower alkyl group or a protected hydroxy-lower alkyl group, and R_1, R_2 and R_4 are the same as defined above, if necessary, followed by removing the protecting groups from the product, or

(b) when the compound (I) is a compound of the formula (I) wherein X is —O—, and R_3 is a hydrogen atom, reacting a compound of the formula (II'):



(II')

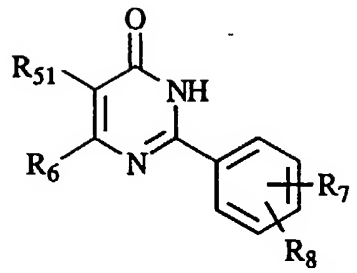
wherein Z_1 is a halogen atom, and R_{51}, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (V):



(V)

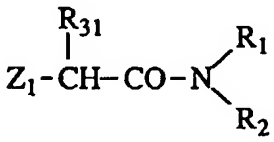
wherein R_1 and R_2 are the same as defined above, and if necessary, followed by removing the protecting groups from the product, or

(c) when the compound (I) is a compound of the formula (I) wherein X is —O—, reacting a compound of the formula (IVa):



(IVa)

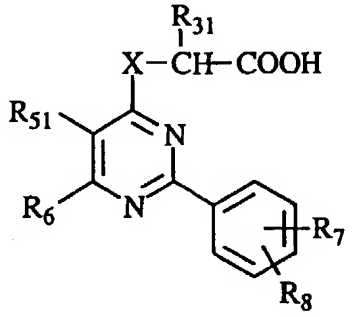
wherein R_{51}, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (VII):



(VII)

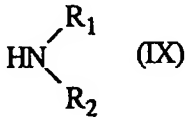
wherein Z_1, R_1, R_2 and R_{31} are the same as defined above, if necessary, followed by removing the protecting groups from the products, or

(d) reacting a compound of the formula (VIII):



(VIII)

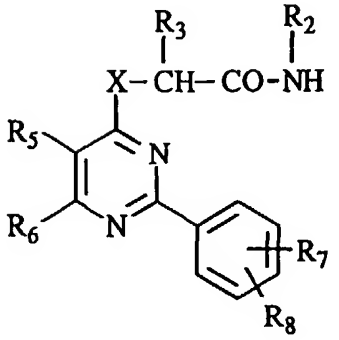
wherein X, R_{31}, R_{51}, R_6, R_7 and R_8 are the same as defined above, or a reactive derivative thereof, with a compound of the formula (IX):



(IX)

wherein R_1 and R_2 are the same as defined above, if necessary, followed by removing the protecting groups from the product, or

(e) when the compound(I) is a compound of the formula (I) wherein R_1 is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group, reacting a compound of the formula (XII):



(XII)

wherein X, R_2, R_3, R_5, R_6, R_7 and R_8 are the same as defined above, with a compound of the formula (XIII):

$$R_{11}—Z_1 \qquad \text{(XIII)}$$

wherein R_{11} is a lower alkyl group, a lower alkenyl group or a cycloalkyl-lower alkyl group, and Z_1 is the same as defined above, if necessary, followed by removing the protecting groups from the product, and if necessary, converting the product thus obtained into a pharmaceutically acceptable acid addition salt thereof.

15. A pharmaceutical composition which contains as an active ingredient the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof.

16. A pharmaceutical composition which contains as an active ingredient the acetamide derivative as set forth in claim 6, or a pharmaceutically acceptable acid addition salt thereof.

17. An agent for treatment of anxiety-related diseases, which contains as an active ingredient the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof.

18. A method for treatment of anxiety-related diseases such as neurosis, somatoform disorders, which comprises administering an effective amount of the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof, to a patient with anxiety-related diseases.

19. Use of the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof, in the treatment of a patient with anxiety-related diseases such as neurosis, somatoform disorders.

20. An anxiolytic agent, which contains as an active ingredient the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof.

21. An agent for treatment of immuno inflammatory diseases, which contains as an active ingredient the acetamide derivatives as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof.

22. A method for treatment of immuno inflammatory diseases, which comprises administering an effective amount of the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof, to a patient with immuno inflammatory diseases.

23. Use of the acetamide derivative as set forth in claim 1, or a pharmaceutically acceptable acid addition salt thereof, in the treatment of a patient with immuno inflammatory diseases.

24. An agent for treatment of immuno inflammatory diseases, which comprises as an active ingredient one of the following compounds:

2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide;
2-(2,6-diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;
2-[5,6-dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide;
2-[2-(4-aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-methyl-N-phenylacetamide; and
2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide,
or a pharmaceutically acceptable acid addition salt thereof.

25. A method for treatment of immuno inflammatory diseases, which comprises administering an effective amount of one of the following compounds;

2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide;
2-(2,6-diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;
2-[5,6-dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide;
2-[2-(4-aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-methyl-N-phenylacetamide; and
2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide, or a pharmaceutically acceptable acid addition salt thereof, to a patient of immuno inflammatory disease.

26. Use of one of following compounds:

2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N,N-dipropylacetamide;
2-(2,6-diphenyl-4-pyrimidinylamino)-N,N-dipropylacetamide;
2-[5,6-dimethyl-2-(4-trifluoromethylphenyl)-4-pyrimidinylamino]-N,N-dipropylacetamide;
2-[2-(4-aminophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-ethyl-N-phenylacetamide;
2-[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyloxy]-N-methyl-N-phenylacetamide; and
2-(5,6-dimethyl-2-phenyl-4-pyrimidinyloxy)-N-phenyl-N-propylacetamide, or a pharmaceutically acceptable acid addition salt thereof, for treatment of a patient of an immuno inflammatory disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/00977

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 C07D239/34, C07D239/42, A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07D239/34, C07D239/42, A61K31/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR, 2263750, A (Delalande S.A.), October 10, 1975 (10. 10. 75)(Family: none)	1-17, 19-21, 23, 24, 26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
June 6, 1996 (06. 06. 96)	July 2, 1996 (02. 07. 96)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/00977

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18, 22, 25
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions of claims 18, 22 and 25 pertain to methods for treatment of the human or animal body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)